# NDA/BLA Multi-Disciplinary Review and Evaluation

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| **Application Type** | BLA |
| **Application Number(s)** | 761122 |
| **Priority or Standard** | Standard |
| **Submit Date(s)** | August 7, 2018 |
| **Received Date(s)** | August 7, 2018 |
| **PDUFA Goal Date** | June 7, 2019 |
| **Division/Office** | Division of Pulmonary, Allergy and Rheumatology Products |
| **Review Completion Date** | May 31, 2019 |
| **Established/Proper Name** | Nucala |
| **(Proposed) Trade Name** | Mepolizumab |
| **Pharmacologic Class** | interleukin-5 antagonist monoclonal antibody (IgG1 kappa) |
| **Code name** | SB240563 |
| **Applicant** | GlaxoSmithKline |
| **Dosage form** | Solution |
| **Applicant proposed Dosing Regimen** | Injection single-dose, prefilled autoinjector or single-dose prefilled syringe |
| **Applicant Proposed Indication(s)/Population(s)** | • Add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype<br>• The treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA) |
| **Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication** | • None proposed |
| **Recommendation on Regulatory Action** | Approval |
| **Recommended Indication(s)/Population(s)** (if applicable) | • Add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype<br>• The treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA) |
| **Recommended SNOMED CT Indication Disease Term for Each Indication** (if applicable) | • Eosinophilic asthma<br>• Eosinophilic granulomatosis with polyangiitis |
| **Recommended Dosing Regimen** | Unchanged – 100 mg Q4 weeks SC for severe asthma, and with an eosinophilic phenotype; 300 mg Q4 weeks SC for EGPA |

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## Reviewers of Multi-Disciplinary Review and Evaluation

| | |
|---|---|
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| **Nonclinical Team Leader** | Tim Robison, PhD |
| **Office of Clinical Pharmacology Reviewer(s)** | Renu Singh, PhD |
| **Office of Clinical Pharmacology Team Leader(s)** | Bhawana Saluja, PhD |
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OBP = Office of Biotechnology Products
OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis

## Signatures

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## Glossary

| | |
|---|---|
| ADA | anti-drug antibody |
| AE | adverse event |
| AI | autoinjector |
| BE | bioequivalence |
| BLA | biologics license application |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| CMC | chemistry, manufacturing, and controls |
| DARRTS | Document Archiving, Reporting, and Regulatory Tracking System |
| DHOT | Division of Hematology Oncology Toxicology |
| DPV-I | Division of Pharmacovigilance I |
| [redacted] | (b) (4) |
| EDTA | ethylenediaminetetraacetic acid |
| EGPA | eosinophilic granulomatosis with polyangiitis |
| FAERS | FDA Adverse Event Reporting System |
| FDA | Food and Drug Administration |
| GSK | GlaxoSmithKline LLC |
| ICH | International Conference on Harmonisation |
| ICS | inhaled corticosteroid |
| IFU | Instructions for Use |
| IL5 | interleukin-5 |
| IND | investigational new drug |
| LABA | long-acting beta agonist |
| mAb | monoclonal antibody |
| NAb | neutralizing antibody |
| NDA | new drug application |
| PB-Eos | peripheral blood eosinophil (PB-Eos) |
| PD | pharmacodynamics |
| PFS | prefilled syringe |
| PK | pharmacokinetics |
| RH | relative humidity |
| SAE | serious adverse event |
| SC | subcutaneous |
| SSD | safety syringe device |
| URTI | upper respiratory tract infection |
| VAS | visual analogue scale |

# 1 Executive Summary

## 1.1. Product Introduction

Mepolizumab is a monoclonal antibody (mAb) directed against interleukin-5 (IL5) that binds IL5 and prevents its interaction with the IL5 receptor, modulating IL5 signaling; this modulation of IL5 signaling leads to decreased eosinophil maturation and survival as well as effects on other Th2 effector cells. Mepolizumab as a lyophilized powder in a single-dose vial for reconstitution is approved under the trade name Nucala (BLA 125526) as a subcutaneous (SC) injection for add-on treatment of severe asthma with eosinophilic phenotype in patients ≥12 years of age and for treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).

This biologics license application (BLA) (761122) is for new liquid formulation presentations of Nucala (mepolizumab) in a prefilled safety syringe device (SSD) and autoinjector (AI). The Applicant is seeking the same dosages, route of administration (SC), and indications for the new SSD and AI presentations as the approved lyophilized drug product.

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

The overall recommended regulatory action for BLA 761122 is Approval. To support the clinical safety and effectiveness of the proposed Nucala prefilled AI and SSD, the development program relied primarily on the demonstration of bioequivalence (BE) between the approved lyophilized Nucala for injection and the proposed AI and SSD liquid formulation presentations. The Applicant conducted Study 204958 which showed that the 90% confidence intervals (CIs) for the primary pharmacokinetics (PK) parameters of $C_{max}$, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ for the respective adjusted treatment ratios (test to reference) were contained within the conventional BE boundaries of 0.80, 1.25 and therefore demonstrated BE between the liquid drug product in an AI or an SSD and the approved lyophilized drug product.

The Applicant also submitted reports of two actual use studies to evaluate administration of the prefilled AI and SSD outside the clinic setting (i.e., home use with administration by the patient or caregiver). In the two actual use studies, subjects with severe eosinophilic asthma received 100-mg SC mepolizumab liquid drug product in a prefilled AI (Study 204959) or a prefilled SSD (Study 205667) self-administered in the thigh or abdomen, or in the upper arm by a caregiver once every 4 weeks for three doses. In-clinic training with the Instructions for Use (IFU) was provided to the subjects or caregivers at the first dose administration, and the remaining two doses were self/caregiver-administered. All subjects successfully self-administered or administered by caregivers with the proposed liquid drug product prefilled AI or SSD. Patient-reported clinical outcome data for actual use studies showed that 98 percent of subjects or caregivers reported that they were "satisfied" with the use of AI or SSD.

No new safety signals were observed in the PK/BE or actual use studies. A total of 238 subjects (79 healthy volunteers and 159 patients with asthma) were exposed to Nucala injection prefilled AI, and 136 subjects (80 healthy volunteers and 56 patients with asthma) were exposed to Nucala

injection prefilled SSD. The adverse events reported from the three studies revealed no new safety signals. The overall evaluation of the clinical studies supports the safety and effectiveness of the proposed new liquid formulation presentations of Nucala (mepolizumab) in prefilled AI and SSD for the treatment of patients with severe eosinophilic asthma or EGPA. To support proposed labeling for home use, the Applicant was asked to submit analyses of hypersensitivity events (including anaphylaxis) from the mepolizumab clinical development program for all indications and from post-marketing experience. Based on the data, the risk of systemic allergic/hypersensitivity reactions is low with the majority of events occurring within the first three dose exposures. Hypersensitivity reactions are currently labeled as a Warnings and Precaution in the Nucala prescribing information. This review concludes that the potential risk of hypersensitivity reactions in a severe asthma population may be mitigated through labeling which states that physicians should determine the appropriateness of self-administration following proper training in injection technique.

## 1.3. Benefit-Risk Assessment

**Benefit-Risk Summary and Assessment**

Nucala (mepolizumab), approved under BLA 125526, is currently provided as a lyophilized powder in a single-dose vial for reconstitution. The present BLA (761122) is for new liquid formulation presentations of Nucala (mepolizumab) in prefilled autoinjector and safety syringe. The Applicant is seeking the same dosages, route of administration (SC), and indications for the new prefilled autoinjector and safety syringe.

This BLA is primarily based on demonstration of bioequivalence (BE) to the approved Nucala for injection to assess the efficacy and safety of the proposed drug product Nucala injection prefilled autoinjector and safety syringe. The Applicant conducted a clinical pharmacology study that demonstrated BE between the liquid drug product in an autoinjector or a safety syringe and the approved lyophilized drug product. The Applicant also conducted two actual use studies to assess the use of the proposed liquid drug product prefilled autoinjector and safety syringe outside the clinic setting. All subjects successfully self-administered or administered by caregivers with the proposed liquid drug product prefilled autoinjector or safety syringe. Patient-reported clinical outcome data for actual use studies showed overall positive perceptions with the new presentations and home use.

No new safety signals were observed in the clinical studies or postmarketing data included in this submission. The overall risk-to-benefit assessment of the new liquid formulation presentations of Nucala (mepolizumab) in prefilled autoinjector and safety syringe is favorable and supports Approval.

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • Asthma is characterized by recurring symptoms of wheezing, breathlessness, chest tightness and coughing caused by underlying airway inflammation and airway hyper-responsiveness. Episodic increases in symptoms are referred to as asthma exacerbations. The disease is typically associated with variable and reversible airflow obstruction, but progressive airway remodeling may lead to persistent asthma associated with partially or fully irreversible airway obstruction leading to chronic symptoms despite standard inhalation treatments. While many exacerbations may be managed as outpatient with use of oral corticosteroids, severe exacerbations may require hospitalization and may even lead to death.<br>• Severe uncontrolled asthma accounts for approximately 5% of all patients with asthma. While there are no clinical guidelines that specifically define 'severe asthma with an eosinophilic phenotype', the estimated prevalence is ≤ 3% of all patients with asthma. | While asthma is a common condition, severe asthma with an eosinophilic phenotype represents a small percentage of the overall asthma population. Nonetheless, patients with severe uncontrolled asthma experience the greatest burden of disease with significant morbidity and deleterious effects on quality of life and daily activity as well as potential for mortality. |
| Current Treatment Options | • For severe asthma with an eosinophilic phenotype, there are three approved biologic therapies (two against IL5, one against IL4Rα) with varying dosing regimens (every 2 weeks up to every 8 weeks), routes of administration (SC and IV), and administration requirements (healthcare professional vs patient/caregiver). | While there are three approved therapies for this specific subset of asthma patients, the availability of additional treatment options is preferable for those unable to tolerate existing treatments. In addition, providing another option for self-administration and home use is desirable for patient convenience. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Benefit | • The effectiveness of mepolizumab for the add-on treatment of severe asthma with an eosinophilic phenotype was demonstrated previously in the initial approval for the lyophilized presentation under BLA 125526.<br>• Bioequivalence between the approved lyophilized presentation of mepolizumab and the new liquid formulations in prefilled autoinjectors and safety syringe devices was established in Study 204958.<br>• Self-administration (or caregiver administration) at home provides ease of use | Mepolizumab is effective for adolescent and adult patients with eosinophilic asthma. New liquid formulations available in autoinjectors and safety syringe devices are bioequivalent to the approved lyophilized presentation. Making autoinjectors and safety syringe devices available to patients for self-administration and home use provides a more convenient method for dosing. |
| Risk and Risk Management | • Hypersensitivity reactions, including anaphylaxis, are a known risk with monoclonal antibodies/biologics.<br>• The frequency of hypersensitivity reactions with mepolizumab is low.<br>• Device malfunction/failure is a potential risk, especially with autoinjectors (AI). Based on available data at 6 and 12 months, the AI injection time appears to increase (take longer) over time, approaching the labeled upper limit of 15 seconds. | A comprehensive review of all available mepolizumab safety data (clinical trials and postmarketing) did not raise concerns about allowing self-administration and home use. The risks of hypersensitivity reactions and improper use of the AI and SSD devices can be managed through labeling and routine pharmacovigilance. Both devices will be approved with a 24-month shelf-life; however, further assessments of the AI injection time will be obtained in a post-marketing commitment (PMC). |

## 1.4. Patient Experience Data

**Patient Experience Data Relevant to This Application** (check all that apply)

| | | | | |
|---|---|---|---|---|
| x | **The patient experience data that were submitted as part of the application include:** | | | **Section of review where discussed, if applicable** |
| | x | Clinical outcome assessment (COA) data, such as | | Section 8.1 |
| | | x | Patient-reported outcome (PRO) | Section 8.1 |
| | | □ | Observer-reported outcome (ObsRO) | |
| | | x | Clinician-reported outcome (ClinRO) | Section 8.1 |
| | | □ | Performance outcome (PerfO) | |
| | □ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | | |
| | □ | Patient-focused drug development or other stakeholder meeting summary reports | | |
| | □ | Observational survey studies designed to capture patient experience data | | |
| | □ | Natural history studies | | |
| | □ | Patient preference studies (e.g., submitted studies or scientific publications) | | |
| | □ | Other: (Please specify): | | |
| □ | **Patient experience data that were not submitted in the application, but were considered in this review:** | | | |
| | □ | Input informed from participation in meetings with patient stakeholders | | |
| | □ | Patient-focused drug development or other stakeholder meeting summary reports | | |
| | □ | Observational survey studies designed to capture patient experience data | | |
| | □ | Other: (Please specify): | | |
| □ | **Patient experience data was not submitted as part of this application.** | | | |

# 2 Therapeutic Context

## 2.1. Analysis of Condition

Asthma is characterized by recurring symptoms of wheezing, breathlessness, chest tightness and coughing caused by underlying airway inflammation and airway hyper-responsiveness. The diagnosis and management of asthma are outlined in several consensus documents: Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma (National Asthma Education and Prevention Program 2007) and the Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention, updated 2018 (Global Initiative for Asthma 2018).

While the majority of patients are managed successfully with a step-wise treatment approach, a subset of patients remains uncontrolled despite maximal medical management and are considered to have a severe refractory asthma. The updated international European Respiratory Society/American Thoracic Society severe asthma guidelines (Chung et al. 2018) define severe asthma as asthma phenotypes based on the recognizable clinical and/or pathophysiological characteristics. The updated Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention recommends add-on anti-IL5 or anti-IL5 receptor treatment for patients ≥12 years of age with severe asthma with an eosinophilic phenotype (Global Initiative for Asthma 2018).

## 2.2. Analysis of Current Treatment Options

For patients with severe asthma who remain symptomatic despite optimal doses of inhaled corticosteroids (ICS) and long-acting beta-agonists (LABA), there are a limited, but growing, number of add-on therapeutic treatment options. Spiriva (tiotropium) Respimat is an inhaled anticholinergic (aka long-acting muscarinic antagonist or LAMA) approved as a bronchodilator for maintenance treatment of asthma in patients 6 years of age and older. Traditionally, oral corticosteroids have been used to treat asthma refractory to approved therapies. Biologic therapies include Xolair (omalizumab) an anti-IgE mAb for allergic asthma phenotypes in patients 6 years and older as well as several recent approvals for asthma patients with an eosinophilic phenotype. Currently there are four FDA-approved, mAb for the add-on treatment of severe asthma with an eosinophilic phenotype (characterized by peripheral blood eosinophilia).

Nucala (mepolizumab) was the first anti-IL5 mAb approved in 2015 (BLA 125526); the initial approval was for a lyophilized powder in a single-dose vial for reconstitution. Nucala is indicated for add-on maintenance treatment of patients ≥12 years of age with severe asthma with an eosinophilic phenotype, and for treatment of adult patients with EGPA.

Cinqair (reslizumab), approved in 2016 (BLA 761033), is an anti-IL5 mAb indicated for add-on maintenance treatment of patients ≥18 years of age with severe asthma with an eosinophilic phenotype. Of note, Cinqair is only available for intravenous infusion by a healthcare professional and contains a boxed warning for anaphylaxis in the product label.

Fasenra (benralizumab), approved in 2017 (BLA761070), is an anti-IL5 receptor mAb indicated for add-on maintenance treatment of patients ≥12 years of age with severe asthma with an eosinophilic phenotype. The dosing regimen for Fasenra is every 4 weeks for the first 3 doses and then once every 8 weeks thereafter administered SC by a healthcare professional. Fasenra is not yet approved for home-use.

Dupixent (dupilumab), approved in 2018 (BLA761055), is an anti-IL4 receptor alpha subunit mAb indicated for add-on maintenance treatment of patients with moderate to severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma. Dupixent is also approved for the treatment of moderate to severe atopic dermatitis not adequately controlled with topical therapies in patients 12 years of age and older. The dosing regimen for Dupixent is every 2 weeks; self-administration with a prefilled syringe (PFS) by patients/caregivers is allowed after proper training at the discretion of the treating physician.

For patients with EGPA, Nucala is the only FDA-approved therapy; however, systemic corticosteroids and other immunosuppressants (e.g., cyclophosphamide, rituximab, azathioprine, methotrexate, mycophenolate mofetil) are frequently used to induce or maintain remission of disease.

# 3 Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

Nucala (mepolizumab) is a currently marketed product in the United States as a lyophilized powder in a single-dose vial for reconstitution. Nucala is indicated for add-on maintenance treatment of patients ≥12 years of age with severe asthma with an eosinophilic phenotype, and for treatment of adult patients with EGPA. This BLA (761122) is for new liquid formulation presentations of Nucala (mepolizumab) in a prefilled safety syringe device (SSD) and autoinjector (AI). The Applicant is seeking the same dosages, route of administration (SC), and indications for the new SSD and AI presentations as the approved lyophilized product.

## 3.2. Summary of Presubmission/Submission Regulatory Activity

Table 1 summarizes the presubmission regulatory activity pertinent to the clinical development program of this BLA.

**Table 1. Summary of Presubmission Regulatory Activity for BLA 761122**

| Date | Meeting and Activity | Topic and Comments |
|---|---|---|
| 04/12/2016 | [redacted] (b) (4) | |
| 11/07/2016 | | |

| Date | Meeting and Activity | Topic and Comments |
|---|---|---|
| 11/14/2016 | Protocol submitted for AI and SSD program (IND 006971) | Submitted protocol for Study 204958 for an open-label, randomized, three-arm, single-dose, multicenter, parallel-group study in healthy subjects to compare the pharmacokinetics of subcutaneous mepolizumab when delivered as a liquid drug product in a safety syringe or an autoinjector with a reconstituted lyophilized drug product from a vial. |
| 12/05/2017 | Agreed iPSP (IND 006971) | Final agreed iPSP for asthma (BLA 125526) |
| 02/27/2018 | Type B, Pre-BLA (IND 006971) | To discuss the proposed submission of the BLA for the liquid drug product of mepolizumab administered via safety syringe and autoinjector devices. |
| 04/11/2018 | Type C, CMC (IND 006971) | To discuss the CMC information for the BLA for the liquid drug product of mepolizumab administered via safety syringe and autoinjector devices. |

BLA = biologics license application, IND = investigational new drug, iPSP= initial Pediatric Study Plan, CMC = chemistry, manufacturing, and controls

# 4 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

## 4.1. Office of Scientific Investigations

Given the nature of this program, clinical study site investigations were not requested for this BLA review.

## 4.2. Product Quality

Mepolizumab is a human IgG1κ monoclonal antibody produced in CHO cells. While the formulation is different than that of the lyophilized product in order to support the stability of the liquid PFS presentation, the drug substance in the approved formulation and the proposed formulation are essentially unchanged. BLA 761122 cross-references BLA 125526 because the (b) (4) are identical. The mepolizumab drug product described in this BLA is supplied at 100 mg/1.0 mL as a sterile, single-dose, preservative-free solution for SC injection in a PFS. The mepolizumab drug product primary container and closure consists of a 1-mL long Type (b) (4) glass (b) (4) barrel with a staked 29-gauge thin-wall x 12.7 mm stainless steel needle with a (b) (4) needle shield covered by rigid plastic shield sealed with (b) (4) rubber plunger stopper.

Filling of the primary syringe container is performed at the (b) (4) manufacturing facility in (b) (4) where the prefilled syringes are then assembled into autoinjectors or safety syringe devices. The autoinjector consists of two subassembly components (syringe unit and drive unit) that are assembled together with the prefilled syringe.

The safety syringe consists of three components (needle guard, plunger rod, and a finger flange) which are assembled together with the prefilled syringe. In both formats, the drug product contacts only the prefilled syringe components.

The data submitted in this application are adequate to support the conclusion that the manufacture of mepolizumab liquid drug product is well-controlled and leads to a product that is pure and potent. Readers may refer to separate product quality reviews for additional details regarding the product quality assessment.

The overall recommended regulatory action from the Office of Product Quality, CDER, is Approval.

## 4.3. Clinical Microbiology

The clinical microbiology review recommends Approval. The microbiology product quality and sterility assurance of the drug substance and drug product submitted to this BLA are acceptable with a postmarketing commitment (PMC) to conduct a microbial retention study. Refer to separate product quality microbiology reviews of the drug substance and drug product for additional details.

## 4.4. Devices and Companion Diagnostic Issues

No companion diagnostic issues were submitted as part of this BLA (761122).

Although the Applicant submitted adequate data to support the stability and function of the AI and SSD devices for the proposed 24-month shelf-life, some data for the autoinjector device suggested an upward trend of delivery time from 6 month to 12-month endpoints (e.g. 6-month range of 9.7 - 11.7 seconds vs 12-month range of 9.1 - 13.7 seconds). Given that trend, the Applicant will provide dose accuracy, injection time, and activation force for the remaining 18 month and 24 month timepoints for ongoing stability protocol on the three (b) (4) batches used to verify of the autoinjector functionality after aging as a PMC.

Refer to the separate CDRH review of the autoinjector and safety syringe devices for details.

# 5 Nonclinical Pharmacology/Toxicology

## 5.1. Executive Summary

The recommended regulatory action from the pharmacology/toxicology review is Approval.

Excipients in the proposed mepolizumab prefilled syringe drug product differ from the reconstituted lyophilized powder in the currently approved product as follows:

- Citrate acid monohydrate replaced [redacted (b) (4)]
- EDTA (ethylenediaminetetraacetic acid) disodium dihydrate was added [redacted (b) (4)]

No safety concerns with respect to systemic or local toxicity were identified with the introduction of citrate acid monohydrate and EDTA disodium dihydrate to the formulation.

The [redacted (b) (4)] is used with multiple approved biologic products. The Applicant conducted extractables and leachables studies with the primary container closure system (prefilled syringe). There were no safety concerns for identified volatile, semi-volatile, and non-volatile leachables.

Additional characterization testing will be performed to update the leachable data with the 5°C/ambient condition for 18, 24, and 36 months and the 30°C/35% relative humidity (RH) condition for 12 months.

No labeling changes were proposed for nonclinical sections of the product label.

## 5.2. Referenced NDAs, BLAs, DMFs

- IND 006971 (GlaxoSmithKline (GSK); mepolizumab for asthma, chronic obstructive pulmonary disease (COPD), EGPA, nasal polyposis (NP); mepolizumab liquid drug product)
- [redacted (b) (4)]
- BLA 125526 (GSK; mepolizumab for severe asthma with an eosinophilic phenotype, EGPA)
- DMF [redacted (b) (4)]
- DMF [redacted (b) (4)]
- MAF [redacted (b) (4)]

- [redacted] (b) (4)

## 5.3. Drug Formulation

Mepolizumab injection, 100 mg/mL, is provided as a sterile solution for SC injection in a single-dose PFS.

**Table 2. Composition of Mepolizumab Injection, 100 mg/mL**

| Ingredient | Quantity (mg per dose) | Function | Quality Standards |
|---|---|---|---|
| Mepolizumab (SB240563) | 100 | Active Ingredient | [redacted] (b) (4) |
| Sucrose | 120.0 | [redacted] (b) (4) | Ph. Eur./USNF/JP |
| Sodium phosphate dibasic heptahydrate | 4.16 | | USP |
| Citric Acid Monohydrate | 0.95 | | Ph. Eur./USP/JP |
| Polysorbate 80 | 0.20 | | Ph. Eur./USNF/JP |
| EDTA Disodium Dihydrate | 0.019 | | USP/ Ph. Eur./BP/JP |
| [redacted] (b) (4) | | | |

**Notes:**
[redacted] (b) (4)
USP = United States Pharmacopeia
Ph. Eur. = European Pharmacopeia
JP = Japanese Pharmacopeia
BP = British Pharmacopeia
USNF = United States National Formulary
Excerpted from Applicant's submission

The primary container and closure, used with the mepolizumab drug product, consists of the following components:

- 1-mL long Type [redacted] (b) (4) glass [redacted] (b) (4) barrel with a staked 29-gauge thin-wall x 12.7 mm stainless steel needle
- [redacted] (b) (4) needle shield covered by rigid plastic shield
- [redacted] (b) (4) plunger stopper made of [redacted] (b) (4) rubber [redacted] (b) (4)

**Figure 1. Appearance of Prefilled Syringe in Primary Packaging**


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**Table 3. Primary Packaging: Components of the Assembled, Mepolizumab Prefilled Syringe and Identity of Materials of Construction**

| Component | Subcomponent | Supplier | Material Description | Color | Function |
|---|---|---|---|---|---|
| Syringe | Glass barrel | [redacted] (b) (4) | | Colorless transparent | Container closure, [redacted] (b) (4) surface reduces friction to enable plunger stopper to move through the barrel during delivery |
| | Staked hypodermic needle | | | Grey (Stainless steel) | Penetrates the skin into the subcutaneous space and enables flow of product for subcutaneous injection |
| | Rigid needle shield (RNS) – insert | | | Black | Maintains container closure integrity<br>Protects needle from damage |
| | Rigid needle shield (RNS) – outer cover | | | Colorless translucent | Protects needle and prevents it from penetrating through the insert and causing accidental needle sticks |
| Plunger stopper | | | | [redacted] (b) (4) | Maintains container closure integrity and enables movement for injection of product |

**Note:**
Abbreviations: [redacted] (b) (4) Rigid Needle Shield (RNS); [redacted] (b) (4)

Excerpted from Applicant's submission, Table 1 Primary Container Closure—Syringe Materials and Function

## Secondary Packaging

The secondary packaging is not in contact with the drug solution. The PFS is assembled into either an autoinjector or a safety syringe device. It consists of two elements:

- Functional passive safety device
- Protective but otherwise nonfunctional outer packaging

The autoinjector is comprised of an opaque housing with a transparent clear inspection window, a yellow needle guard, and a translucent cap.

**Figure 2. External Appearance and Components of the Autoinjector**


| Subassembly Component | Individual Component Name | Material of Construction | Color | Function |
|---|---|---|---|---|
| | | | | (b) (4) |

Note:
1. Component with potential patient contact and therefore subjected to biocompatibility testing.

Excerpted from Applicant's submission

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The safety syringe device is comprised of a needle guard, a plunger rod, and a finger flange as shown in Figure 3.

**Figure 3. External Appearance and Components of the Safety Syringe Device**

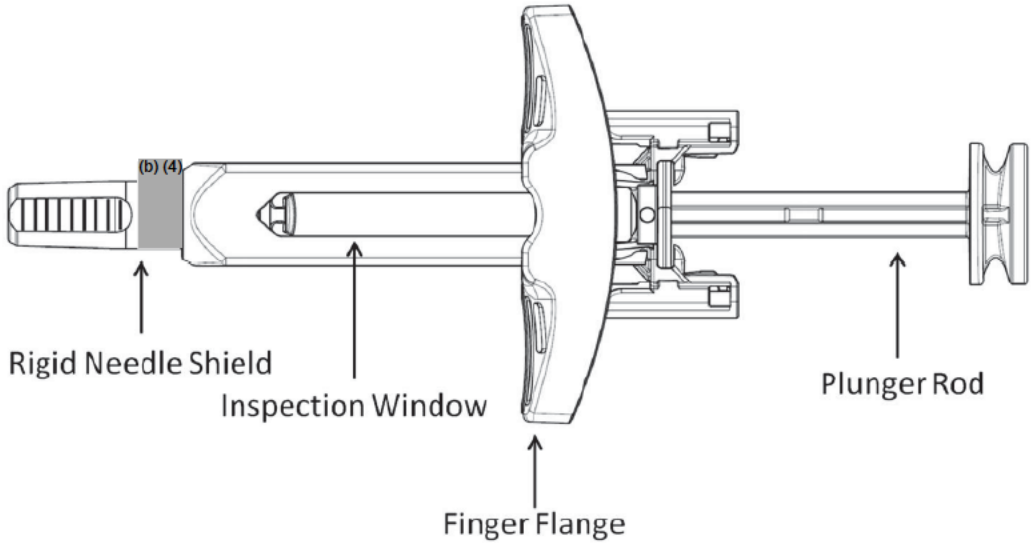


**Table 4. Materials of Construction for Safety Syringe Components**

| Subassembly Component | Individual Component Name | Material of Construction | Color | Function |
|---|---|---|---|---|
| Needle Guard | Body[1] | (b) (4) | Colorless/ transparent | Holds the syringe during injection and when the device is activated moves with the syringe to enable the exposed needle to be shielded in the guard component. |
| | Guard[1] | | Colorless/ transparent | Interfaces with the plunger rod to activate the needle shielding mechanism and forms the guard which shields the exposed needle. |
| | Spring | Stainless Steel | Not Applicable | Facilitates retraction of body (and syringe) into the guard to shield the needle of the syringe. |
| Plunger Rod[1] | Not Applicable | (b) (4) | White | Attaches to the plunger stopper in the syringe to enable the patient to dispense the medication. Interfaces with the body to activate the shielding mechanism. |
| Finger Flange[1] | Not Applicable | | White | Allows the patient to better grip the device when pushing the plunger rod to deliver the dose. |

**Notes:**
1. Component with potential patient contact and therefore subjected to biocompatibility testing.

Excerpted from Applicant's submission

## 5.4. Comments on Novel Excipients

Excipients in the proposed mepolizumab PFS drug product differ from the reconstituted lyophilized powder in the currently approved product as follows:

- Citrate acid monohydrate replaced [redacted (b) (4)]
- EDTA disodium dihydrate was added [redacted (b) (4)]

**Table 5. Composition of Mepolizumab for Injection in Prefilled Syringe and Mepolizumab Powder for Solution for Injection**

| Ingredient | Quantity (mg per 100 mg nominal dose) | |
|---|---|---|
| | Mepolizumab for Injection (100 mg Lyophilized Drug Product in Vial)[1] | Mepolizumab Injection (100 mg Liquid Drug Product in AI or SSD) |
| Mepolizumab | 100 | 100 |
| Sucrose | [redacted (b) (4)] | 120 |
| Sodium phosphate dibasic heptahydrate | | 4.16 |
| Citrate Acid Monohydrate | N/A | 0.95 |
| Polysorbate 80 | [redacted (b) (4)] | 0.2 |
| EDTA Disodium Dihydrate | N/A | 0.019 |
| [redacted (b) (4)] | | |

Excerpted from Applicant's submission, Table 1 Summary of the Difference in Excipient Quantities Between the Commercial, Lyophilized and Proposed Liquid Drug Product Formulations

Citrate acid monohydrate is present at a dose of 0.95 mg in the maximum dose of mepolizumab at 100 mg once every 4 weeks. Citrate acid is a naturally occurring constituent of plant and animal tissues. It is a direct food substance affirmed as "generally recognized as safe" (21CFR184.1033). Citrate acid is an excipient in products approved by the U.S. Food and Drug Administration (FDA) for parenteral administration, including the SC route, in lower amounts to that in the Humira® (SC route; 9.6 mg citrate acid in 40 mg adalimumab biweekly). Therefore, no safety concerns with respect to systemic or local toxicity were identified with the introduction of citrate acid monohydrate to the formulation.

EDTA disodium dihydrate is present at a dose of 0.019 mg in the maximum dose of mepolizumab at 100 mg once every 4 weeks. EDTA is a chemical used for both industrial and medical purposes. It is produced as several salts, notably disodium EDTA and calcium disodium EDTA. Both salt forms of EDTA are food additives (21CFR573.360 for disodium EDTA and 21CFR172.120 for calcium disodium EDTA). EDTA is an excipient in FDA-approved products for parenteral administration, including the SC route, in lower amounts to that in the Adrenalin® [SC route; 0.1 mg EDTA in 0.5 mg epinephrine]. Therefore, no safety concerns with respect to systemic or local toxicity were identified with the introduction of EDTA disodium dihydrate to the formulation.

## 5.5. Regulatory Background

Under IND 006971, a Type B pre-BLA meeting was held with the Applicant on February 27, 2018. The following nonclinical comment was conveyed to the Applicant.

**Nonclinical Comment**

Provide the actual reports of extractables and leachables studies with the application.

An information request was sent on September 11, 2018, to obtain the reports of the extractables and leachables studies. The reports were submitted to the BLA on September 19, 2018.

## 5.6. Studies Reviewed

Extractables and Leachables Studies were described in the following documents:

- Module 2.3
- Module 3.2.P.1 Description and Composition of the Drug Product
- Module 3.2.P.2.4 Container Closure System Development
- Module 3.2.P.7 Container Closure System
- Leachable Summary for Mepolizumab Drug Product (DP) in Pre-filled Syringe, Document No. 2018N370506v1, Report Title "SB-240563 Summary Report Detailing the Long-Term Leachable Results for Mepolizumab Solution for Injection Drug Product." (Pre-filled Syringe); submitted on September 19, 2018
- Technical Risk Assessment on Potential Sources of Leachables from Mepolizumab Liquid (b) (4) Document No. 2018N358165v1; submitted on September 19, 2018

## 5.7. Evaluation of Extractables and Leachables Studies

The proposed liquid drug product mepolizumab injection is provided as 100-mg/1-mL solutions intended for SC administration. The container closure system for mepolizumab injection is composed of a prefilled syringe as the primary container which is assembled into an autoinjector or a safety syringe device. The primary container closure system in the prefilled syringe configuration consists of a 1-mL long USP Type (b) (4) glass barrel (b) (4) with staked 29-gauge x ½-inch thin-wall needle, sealed by a rigid needle shield composed of a (b) (4) outer cover, and a (b) (4) rubber plunger stopper (b) (4) (b) (4)

**Extractables Characterization**

Only summary results for the extractable study were provided by the Applicant. Detailed methods for analysis and identification were not provided.

[redacted] is used with many approved biologic products. The risk for the leachables from the syringe or needle is low with stainless steel and Type [redacted] glass. The needle guard is a 510K approved product [redacted] The autoinjector is a 510K approved product [redacted] DMF [redacted] was cross-referenced. Extractable studies of volatile compounds were conducted for the plunger stopper and needle shield. Four different extraction methods were used to assess extractables:

A. Samples were heated at 150°C for 40 minutes in sealed headspace vials
B. Closed vessel extraction at 90°C for 133 hours with [redacted]
C. Closed vessel extraction at 90°C for 133 hours with [redacted]
D. Closed vessel extraction at 90°C for 133 hours with [redacted]

In addition, aliquots from B, C, and D were prepared by liquid/liquid extraction into [redacted]. The [redacted] extracts were analyzed by gas chromatography–mass spectrometry (GC-MS) and ultra liquid chromatography–mass spectrometry (UPLC-MS) for semi-volatile and non-volatile compounds, respectively.

In the needle shield, [redacted] were detected from the [redacted] extraction study at levels above [redacted] mcg/day in the semi-volatile analysis. Volatile and non-volatile compounds were not observed above [redacted] mcg/day in the needle shields.

In the plunger stopper, [redacted] were detected from the [redacted] extraction study at levels above [redacted] mcg/day in the semi-volatile analysis. In addition, [redacted] were detected from the [redacted] extraction study at levels above [redacted] mcg/day in the non-volatile analysis. Volatile compounds were not observed above [redacted] mcg/day in the plunger stopper.

**Leachables Assessed During Stability Studies**

The Applicant did not use the extractable study to establish any target leachables. A study to assess leaching of compounds from the prefilled syringes during 12 months stability studies was carried out for three batches (PQ780817, PQ782189, and PQ785758; 100 mg/mL). [redacted] GC-MS method (M0022778) was used to quantify the volatile leachables. GC-MS method (M0022564) was used to quantify the semi-volatile leachables. High-resolution accurate mass-UPLC-MS method [redacted] protocol reference 1610066) was used to quantify the non-volatile organic leachables. Leachable studies were conducted at two storage conditions (5°C/ambient and 30°C/35% RH). Leachables were identified using library matching in the NIST library.

**Table 6. 12-Month Leachables Stability Protocol for Mepolizumab Injection Drug Product in Prefilled Syringe**

| Condition level | Time (Months) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 3 | 6 | 9 | 12 | 18 | 24 | 36 | 48 | 60 |
| 5°C/Amb | - | (A), (B) | A, (B) | A, (B) | A, B | A, (B) | A, (B) | A, B | (A), (B) | (A), (B) |
| 30°C/35%RH | - | (A), (B) | A, (B) | A, (B) | A, B | - | - | - | - | - |

Amb Uncontrolled Ambient Humidity
RH Relative Humidity
- Denotes testing not scheduled at these timepoints
() Denotes optional testing
A Method: M0022778 and M0022564
B Method: (b) (4) protocol reference 1610066

Excerpted from Applicant's submission, Table 2. Protocol Test Program Batch PQ780817, PQ782189, PQ785758

Results for potential **volatile leachables** are shown in Table 7. (b) (4) was detected in all three batches stored at 5°C/ambient and 30°C/35% RH for 6 and 9 months with a maximum amount of (b) (4) mcg/day. (b) (4) was detected in batch PQ785758 stored at 5°C/ambient for 9 months with a maximum amount of (b) (4) mcg/day. (b) (4) was detected in batch PQ780817 stored at 5°C/ambient for 6 months with a maximum amount of (b) (4) mcg/day. (b) (4) was detected in all three batches stored at 5°C/ambient and 30°C/35% RH for 6, 9, and 12 months with a maximum amount of (b) (4) mcg/day.

**Table 7. Volatile Leachable Levels Detected Above the Reporting Threshold in Three Mepolizumab Drug Product Batches in Prefilled Syringe**

| Storage Condition | Storage Time Months | Batch | (b) (4) |
|---|---|---|---|
| Threshold for detection (µg/day)[1] | | | |
| | | | |
| 5°C/ Ambient | 6 | PQ780817 | |
| | | PQ782189 | |
| | | PQ785758 | |
| | 9 | PQ780817 | |
| | | PQ782189 | |
| | | PQ785758 | |
| | 12 | PQ780817 | |
| | | PQ782189 | |
| | | PQ785758 | |
| 30°C/35% RH | 6 | PQ780817 | |
| | | PQ782189 | |
| | | PQ785758 | |
| | 9 | PQ780817 | |
| | | PQ782189 | |
| | | PQ785758 | |
| | 12 | PQ780817 | |
| | | PQ782189 | |
| | | PQ785758 | |

1 Threshold for detection, identification and quantitation for leachables
2 The mean was calculated over 3 replicates.
3 Maximum level observed per timepoint

Excerpted from Applicant's submission, Table 4. Volatile Leachable Levels Detected Above the Reporting Threshold in Three Mepolizumab DP Batches

**Table 8. [redacted] (b) (4) Levels Detected Above the Reporting Threshold in Three Mepolizumab Drug Product Batches**

| Storage Condition | Storage Time Months | Batch | [redacted] (b) (4) |
|---|---|---|---|
| Threshold for detection (µg/day)[1] | | | |
| | | | |
| 5°C/ Ambient | 6 | PQ780817 | |
| | | PQ782189 | |
| | | PQ785758 | |
| | 9 | PQ780817 | |
| | | PQ782189 | |
| | | PQ785758 | |
| | 12 | PQ780817 | |
| | | PQ782189 | |
| | | PQ785758 | |
| 30°C/35% RH | 6 | PQ780817 | |
| | | PQ782189 | |
| | | PQ785758 | |
| | 9 | PQ780817 | |
| | | PQ782189 | |
| | | PQ785758 | |
| | 12 | PQ780817 | |
| | | PQ782189 | |
| | | PQ785758 | |

1. Threshold for detection, identification and quantitation for leachables
2. The mean was calculated over 3 replicates.
3. Maximum level observed per timepoint

Excerpted from Applicant's submission

For potential **semi-volatile leachables**, [redacted] (b) (4) was detected in one out of three replicates from batch PQ785758 stored at 5°C/ambient for 12 months with a maximum amount of [redacted] (b) (4) mcg/day.

For potential **non-volatile leachables**, no non-volatile compounds above the detection threshold of (b) (4) mcg/day were detected.

The compounds observed in the extractables studies (b) (4) were not detected as leachables above (b) (4) mcg/day in the mepolizumab drug product under the controlled storage conditions. Lack of vigorous extraction with multiple solvents of varying polarity, multiple extraction techniques, and multiple analytical techniques could lead to the under detected results in the extraction studies. Nevertheless, the risk of these extractables to patients is low.

**Additional Container Closure Characterization Testing**

Additional characterization testing will be performed to update the leachable data with the 5°C/ambient condition for 18, 24, and 36 months and the 30°C/35% RH condition for 12 months.

Further research will be performed to get a better understanding of how (b) (4) is formed.

(b) (4) was present above the detection threshold of (b) (4) mcg/day in one of the replicates. The amount was calculated using a relative response factor (RRF) of (b) (4) Additional work will be performed to determine the actual RRF and to confirm the identity of this substance.

## 5.8. Safety Evaluation of Volatile, Semi-volatile, and non-volatile Leachables

(b) (4) was detected in samples stored at 5°C/ambient and 30°C/35% RH with a maximum amount of (b) (4) mcg/day. (b) (4) was detected in samples stored at 5°C/ambient with a maximum amount of (b) (4) mcg/day. (b) (4) was detected in samples stored at 5°C/ambient with a maximum amount of (b) (4) mcg/day. (b) (4) was detected in samples stored at 5°C/ambient and 30°C/35% RH with a maximum amount of (b) (4) mcg/day. (b) (4) was detected in samples stored at 5°C/ambient with a maximum amount of (b) (4) mcg/day.

(b) (4) was not observed during the extraction studies of the drug product container closure system. (b) (4) levels were likely to be due to (b) (4) (b) (4)



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(b) (4)

# 6 Clinical Pharmacology

## 6.1. Executive Summary

The Applicant conducted one relative bioavailability study (Study 204958) to support a new BLA for a liquid formulation (solution, 100 mg/mL) of Nucala (mepolizumab) in a prefilled syringe (PFS) for subcutaneous (SC) use via either an autoinjector (AI, prefilled pen) or a safety syringe device (SSD), intended for administration by patients themselves or caregivers, outside of the health care setting (e.g., patient self-administration at home). The Applicant is proposing the same dosing regimen and indications as the approved lyophilized product (Nucala, BLA 125526).

Study 204958 was an open-label, randomized, three-arm, single-dose, multicenter, parallel-group study in healthy subjects to compare the pharmacokinetics of SC mepolizumab when delivered as a liquid drug product in an SSD or an AI with a reconstituted lyophilized drug product from a vial. The 90% CIs for the geometric mean treatment ratios (liquid drug product in AI versus lyophilized drug product and liquid drug product in SSD versus lyophilized drug product) of mepolizumab $C_{max}$, $AUC_{0-\infty}$, and $AUC_{0-t}$ were all contained within 0.80, 1.25. This demonstrated statistical PK comparability between the liquid drug product (AI or SSD) and the lyophilized drug product. The trough concentrations ($C_{troughs}$) with the liquid drug product (AI or SSD) in patients with severe eosinophilic asthma in Studies 205667 and 204959 were also consistent with the lyophilized drug product (BLA 125526).

From a clinical pharmacology perspective, this BLA (761122) is acceptable and the recommended regulatory action is Approval.

## 6.2. Summary of Clinical Pharmacology Assessment

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed clinical pharmacology information submitted under BLA 761122 and finds the application sufficient to support Approval.

### 6.2.1. Pharmacology and Clinical Pharmacokinetics

The clinical development program included a pivotal study to compare the systemic exposure of mepolizumab for the proposed liquid drug product with the approved lyophilized drug product

(Study 204958) and two actual use studies (Studies 205667 and 204959). For discussion of Actual Use studies refer to the clinical review in Section 8.

Study 204958 was an open-label, randomized, three-arm, single-dose, multicenter, parallel-group study in healthy subjects to compare the pharmacokinetics (PK) of SC mepolizumab when delivered as a liquid drug product in an SSD or an AI with a reconstituted lyophilized drug product from a vial. The primary objectives of the study were to compare the pharmacokinetics [maximum observed plasma drug concentration ($C_{max}$), area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time ($AUC_{0-inf}$), and area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration ($AUC_{0-t}$)] of SC mepolizumab following a single dose of the liquid formulation in either SSD or AI with the lyophilized drug product.

Subjects were randomized 1:1:1 to receive mepolizumab 100-mg SC (approximately 72 per group) either as an SSD (test), an AI (test) or reconstituted lyophilized drug product from a vial (reference). The site of injection was randomized 1:1:1 to the upper arm, abdomen, or thigh (approximately 24 per injection site). The randomization was further stratified by body weight category, <70kg, 70 to <80kg and ≥80kg with at least 27 subjects randomized within each of the three body weight strata, resulting in at least nine subjects within each treatment group and weight strata, subdivided as three subjects within each distinct treatment group, weight strata, and injection site.

The 90% CIs for the geometric mean treatment ratios (liquid drug product in AI versus lyophilized drug product, and liquid drug product in SSD versus lyophilized drug product) of mepolizumab $C_{max}$, $AUC_{0-\infty}$ and $AUC_{0-t}$ were all contained within 0.80, 1.25. This demonstrated statistical PK comparability between the liquid drug product (AI or SSD) and the lyophilized drug product. After SC injection at three different sites (upper arm, abdomen, or thigh), the mean and median mepolizumab plasma concentration-time profiles did not appear to differ markedly, irrespective of the treatment groups. In SSD and AI groups, there was a trend towards slightly lower mepolizumab geometric mean exposure ($C_{max}$ and AUCs) with increased body weight categories (<70 kg, 70 to <80 kg and ≥80 kg), similar to that observed with the lyophilized product used in this study and also seen in the original BLA 125526.

Aside from PK, the PB-Eos count was also measured in this healthy subject PK comparability study. Geometric mean ratios to baseline blood eosinophil count over time (adjusted for baseline blood eosinophil count, injection site [arm, abdomen, thigh], and baseline weight) were similar across the three treatment groups with values of 0.335, 0.344, and 0.311, respectively (i.e., reductions from baseline of 67%, 66%, and 69%, respectively) at Day 29 for lyophilized drug product, liquid drug product in AI, and liquid drug product in SSD, respectively.

Overall, PK comparability of mepolizumab was demonstrated following SC administration using the AI or SSD versus lyophilized drug product.

### 6.2.2. General Dosing and Therapeutic Individualization

**General Dosing**

The recommended dose is 100 mg administered SC once every 4 weeks for asthma and 300 mg SC once every 4 weeks for EGPA.

**Therapeutic Individualization**

The recommended dosage of Nucala is 100 mg or 300 mg administered once every 4 weeks by SC injection into the upper arm, thigh, or abdomen.

**Outstanding Issues**

None

## 6.3. Comprehensive Clinical Pharmacology Review

### 6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Mepolizumab (SB-240563) is a humanized mAb (immunoglobulin G [IgG1], kappa, mAb) that binds with high specificity and affinity to human IL-5, the key cytokine responsible for regulation of blood and tissue eosinophils. Neutralization of IL-5 with mepolizumab produces a reduction of blood eosinophils levels which has been observed in severe asthma and EGPA.

The currently marketed drug product is supplied as a 100-mg single-dose vial containing a sterile, preservative-free, lyophilized powder for reconstitution in sterile water and SC injection by a health care professional. Reconstitution results in a concentration of 100 mg/mL. GSK has developed a liquid drug product, which will be provided as a solution (100 mg/mL) in a prefilled syringe (1-mL (b) (4) glass prefillable syringe) in either an SSD (1.0-mL (b) (4) Passive Needle Guard) or an AI (1.0-mL (b) (4) AI from (b) (4) device.

Following 100-mg SC administration in the upper arm of subjects with severe eosinophilic asthma, the bioavailability of mepolizumab was estimated to be approximately 80%. In subjects with severe eosinophilic asthma, mepolizumab exhibited approximately dose-proportional pharmacokinetics over a dose range of 12.5 to 250 mg. Following repeat SC administration once every 4 weeks, there was a 2-fold accumulation at steady state. Mepolizumab is degraded by proteolytic enzymes widely distributed in the body and not restricted to hepatic tissue. Following SC administration of mepolizumab, the mean terminal half-life ($t_{1/2}$) ranged from 16 to 22 days. The population apparent systemic clearance of mepolizumab in patients with asthma is estimated to be 0.28 L/day for a 70-kg individual.

### 6.3.2. Clinical Pharmacology Questions

**What are the clinical pharmacology studies submitted under this NDA?**

The mepolizumab liquid product clinical development program consisted of the following three clinical studies:

- An open-label, randomized, three-arm, single-dose, multicenter, parallel-group study in healthy subjects to compare the pharmacokinetics of SC mepolizumab when delivered as a liquid drug product in an SSD or an AI with a reconstituted lyophilized drug product from a vial (Study 204958)
- An open-label, single-arm, repeat-dose, multicenter study to evaluate the use of an AI for the SC administration of mepolizumab in subjects with severe eosinophilic asthma (Study 204959)
- An open-label, single-arm, repeat-dose, multicenter study to evaluate the use of an SSD for the SC administration of mepolizumab in subjects with severe eosinophilic asthma (Study 205667)

**Was the to-be-marketed product used for pivotal study?**

A comparison of the liquid and lyophilized formulations is provided in Table 9.

**Table 9. Composition of Lyophilized and Liquid Mepolizumab Drug Products**

| Ingredient | Ingredient Quantity (mg per 100 mg nominal dose) | |
|---|---|---|
| | Lyophilised Product | Liquid Product |
| Active ingredient | 100 | 100 |
| Sucrose (stabilizer, tonicity modifier) | (b) (4) | 120 |
| Sodium phosphate dibasic heptahydrate (buffer) | | 4.16 |
| Citrate Acid Monohydrate (buffer) | N/A | 0.95 |
| Polysorbate 80 (stabilizer, interfacial stress, shear protection) | (b) (4) | 0.2 |
| EDTA Disodium Dihydrate (metal chelating agent) | N/A | 0.019 |
| (b) (4) | | |

Source: Module 2.7.1. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Page 8

The mepolizumab liquid drug product used in clinical studies was manufactured from drug substance that was produced using the commercial drug substance manufacturing process. The prefilled syringes were assembled into AIs (prefilled pens) or SSDs. Devices used in clinical studies were assembled using the commercial automated assembly machine at reduced scale. The

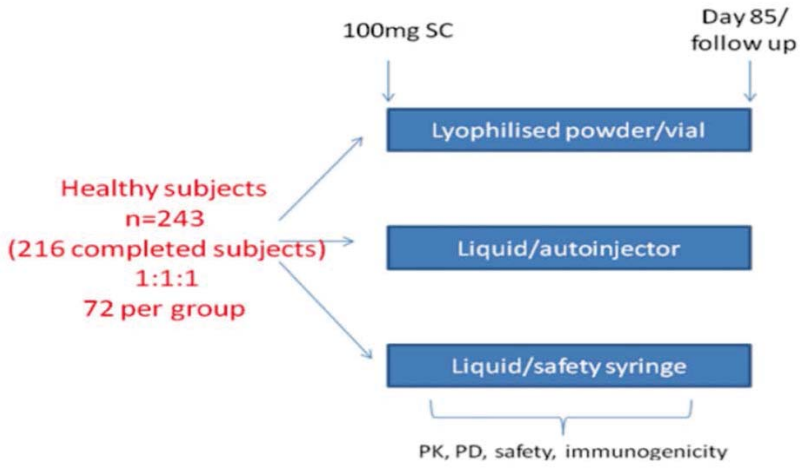
AI and SSD for commercialization remain unchanged in form and function from devices used during development (i.e., in actual use and clinical studies).

**Are the exposures from lyophilized product comparable to the liquid drug product delivered by autoinjector or safety syringe device?**

***Single-dose PK in healthy subjects***

The objective of the Study 204958 was to demonstrate the comparability of mepolizumab PK between the lyophilized drug product and the liquid drug product delivered by SSD or AI, following a single 100-mg SC dose in healthy subjects ≥18 years of age. The study was a randomized, multicenter, open-label, three-arm, parallel-group study stratified by body weight (<70 kg, 70 to <80 kg, and ≥80 kg). Mepolizumab 100-mg SC was administered by a health care practitioner with subjects randomized in a 1:1:1 ratio to one of the following treatment groups: liquid drug product in an SSD, liquid drug product in an AI, or reconstituted lyophilized drug product (approximately 72 per group) (see Figure 4). The site of injection was also randomized in a 1:1:1 ratio to the upper arm, abdomen, or thigh (approximately 24 per injection site). Subjects were followed for 85 days following drug administration for collection of PK, immunogenicity, and pharmacodynamic (PD; blood eosinophil count) samples, and assessment of safety.

**Figure 4. Study Design Schematic**

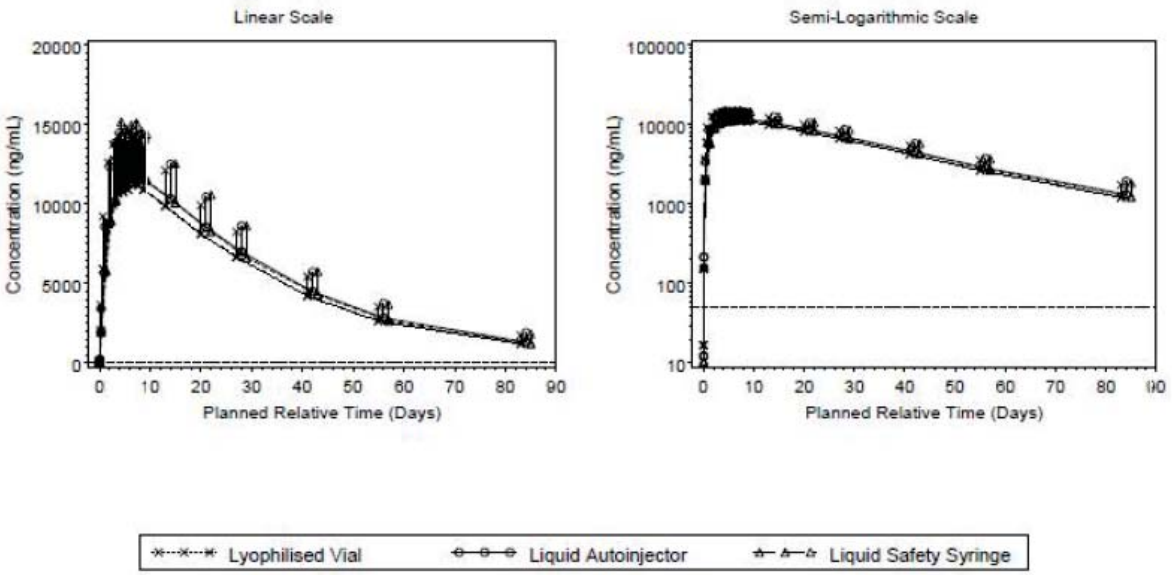



PD = pharmacodynamics

Source: Module 5.3.1.2 Study report 204958, page 19

A total of 244 healthy subjects were enrolled in this study. The PK profiles by treatment groups are shown in Figure 5. The 90% CIs for the geometric mean ratios (liquid drug product in AI versus lyophilized drug product and liquid drug product in SSD versus lyophilized drug product) of mepolizumab $C_{max}$, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}t}$ were all contained within 0.80, 1.25. This demonstrated statistical PK comparability between the liquid drug product (AI or SSD) and the lyophilized drug product (see Table 10). The reviewer conducted independent analysis and the results are comparable to that reported by the Applicant.

**Figure 5. Arithmetic Mean (+SD) Plasma Mepolizumab Concentration-Time Plots by Treatment (Linear and Semi-Log)**




Study 204958, pharmacokinetics population
Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, page 6

**Table 10. Adjusted Mepolizumab PK Exposure Ratios Between Liquid Drug Product in a Safety Syringe or Autoinjector vs. Lyophilized Drug Product in Healthy Subjects Following Single-Dose Administration in Study 204958**

| | Safety Syringe[a] vs. Lyophilized[c] | | | Autoinjector[b] vs Lyophilized[c] | | |
|---|---|---|---|---|---|---|
| **Parameter** | **GMR** | **90% LCI** | **90% UCI** | **GMR** | **90% LCI** | **90% UCI** |
| $AUC_{inf}$ (day*mcg/mL) | 1.02 | 0.95 | 1.09 | 1.07 | 1.00 | 1.13 |
| $AUC_{last}$ (day*mcg/mL) | 1.04 | 0.97 | 1.12 | 1.08 | 1.01 | 1.15 |
| $C_{max}$ (mcg/mL) | 1.06 | 0.99 | 1.12 | 1.04 | 0.98 | 1.11 |

[a] safety syringe N=80
[b] autoinjector N=79
[c] lyophilized N=85
GMR = geometric mean ratio, LCI = lower confidence interval, UCI = upper confidence interval. PK = pharmacokinetics
The estimates of the geometric mean are adjusted for injection site (arm, abdomen, thigh) and baseline weight ($log_e$ scale).
Source: Module 5.3.1.2 Study report 204958, page 52

During review, the following observations were made:

- Pre-dose concentrations <5% of $C_{max}$ were noted in nine subjects.
- Two subjects had pre-dose concentration with values >5% of $C_{max}$ (~6% to 8%).

The Applicant included all subjects for PK analysis. The draft guidance "Bioavailability Studies Submitted in NDAs or INDs—General Considerations" (Food and Drug Administration February, 2019) provides the following recommendation regarding subjects with pre-dose plasma concentrations:

> "If the pre-dose concentration is less than or equal to 5 percent of the $C_{max}$ value in that subject, the subject's data without any adjustments can be included in all PK measurements and calculations. We recommend that if the pre-dose value is greater than 5 percent of the $C_{max}$, the subject should be dropped from all PK evaluations. However, this subject's data should be flagged and reported, and the subject should be included in the safety evaluations."

Accordingly, this reviewer performed additional sensitivity analysis by excluding subjects who had pre-dose concentration with values >5% of $C_{max}$. These analyses met the bioequivalence criterion.

***Effect of injection site***

As part of the PK comparability study, the effect of injection site (upper arm, abdomen, or thigh) on mepolizumab PK profile was also evaluated (approximately 24 subjects per injection site). The systemic exposure of mepolizumab with either the lyophilized drug product or liquid drug product (AI or SSD) was generally comparable across different sites of injection. The within-treatment (i.e., lyophilized, liquid AI and liquid SSD) ratios between highest and lowest geometric mean across the three injection sites ranged from 1.16 to 1.25 for $C_{max}$ and from 1.05 to 1.27 for $AUC_{0\text{-}inf}$ (see Table 11).

**Table 11. Geometric Mean of PK Parameters for Mepolizumab Following Single SC Dose Administration by Various Injection Sites in Healthy Subjects**

| | | Liquid Autoinjector | | Liquid Safety Syringe | | Lyophilized Vial | |
|---|---|---|---|---|---|---|---|
| **Parameter** | ***Site*** | **Geo Mean** | **CV%** | **Geo Mean** | **CV%** | **Geo Mean** | **CV%** |
| $AUC_{inf}$ (day*mcg/mL) | *Abdomen* | 428.49 | 29.75 | 438.17 | 27.79 | 442.66 | 24.62 |
| | *Arm* | 465.22 | 24.29 | 450.74 | 25.74 | 443.97 | 28.09 |
| | *Thigh* | 545.32 | 21.19 | 472.69 | 42.47 | 465.40 | 28.48 |
| $AUC_{last}$ (day*mcg/mL) | *Abdomen* | 392.21 | 28.74 | 402.76 | 27.49 | 382.04 | 40.76 |
| | *Arm* | 423.55 | 21.79 | 413.81 | 23.56 | 402.94 | 25.06 |
| | *Thigh* | 491.43 | 17.87 | 428.27 | 39.28 | 426.97 | 27.42 |
| $C_{max}$ (mcg/mL) | *Abdomen* | 11.27 | 36.15 | 11.48 | 34.7 | 11.44 | 25.14 |
| | *Arm* | 11.04 | 23.11 | 11.44 | 25.21 | 10.75 | 21.49 |
| | *Thigh* | 13.75 | 16.07 | 13.29 | 26.54 | 12.57 | 33.15 |

CV = coefficient of variation, PK = pharmacokinetics, SC = subcutaneous
Source: Reviewer's analysis of data submitted in Module 5.3.1.2 Study 204958

***Effect of body weight***

Bodyweight was stratified in the PK comparability study, in order to evaluate its impact on the PK of mepolizumab (with at least 27 subjects randomized within each of the three body weight strata). Both lyophilized drug product and liquid drug product (AI or SSD) showed a trend for decreased rate and extent of mepolizumab absorption with increased bodyweight categories (<70 kg, 70 to <80 kg and ≥80 kg) (see Table 12).

Since bodyweight is a determinant of mepolizumab exposure, the observed impact was expected and in accordance with previous observations of the lyophilized drug product (refer to clinical pharmacology review BLA 125526 by Dr. Yunzhao Ren dated July 5, 2015, in DARRTS). Using the 70 kg to <80 kg bodyweight category as reference, across treatment groups, geometric mean $C_{max}$ increased between 3% and 15% in the <70 kg category and decreased between 7% and 18% in the ≥80 kg category. The corresponding increase in geometric mean $AUC_{0\text{-}inf}$ ranged from 10% to 16%, and the corresponding decrease ranged from 8% to 22%, respectively. The effect of body weight on PK of mepolizumab is not clinically important given the flatness of dose/exposure relationship for efficacy.

**Table 12. Geometric Mean of PK Parameters for Mepolizumab Following Single SC Dose Administration by Various Weight Categories in Healthy Subjects**

| | | Liquid Autoinjector | | Liquid Safety Syringe | | Lyophilized Vial | |
|---|---|---|---|---|---|---|---|
| **Parameter** | ***Category*** | **Geo Mean** | **CV%** | **Geo Mean** | **CV%** | **Geo Mean** | **CV%** |
| $AUC_{inf}$ (day*mcg/mL) | *<70 kg* | 524.26 | 22.24 | 537.09 | 24.05 | 507.35 | 23.20 |
| | *>=80 kg* | 424.31 | 26.85 | 359.80 | 35.06 | 402.21 | 21.31 |
| | *70-<80 kg* | 475.84 | 28.88 | 463.86 | 25.43 | 435.62 | 30.51 |
| $AUC_{last}$ (day*mcg/mL) | *<70 kg* | 472.36 | 19.38 | 490.46 | 22.54 | 438.69 | 39.88 |
| | *>=80 kg* | 389.53 | 24.94 | 328.57 | 31.89 | 366.2 | 18.48 |
| | *70-<80 kg* | 433.12 | 27.38 | 425.04 | 22.84 | 399.59 | 28.3 |
| $C_{max}$ (mcg/mL) | *<70 kg* | 12.45 | 24.02 | 13.95 | 20.04 | 12.65 | 27.62 |
| | *>=80 kg* | 11.23 | 31.41 | 9.99 | 33.46 | 10.26 | 19.59 |
| | *70-<80 kg* | 12.13 | 28.85 | 12.16 | 25.23 | 11.6 | 30.21 |

CV = coefficient of variation, PK = pharmacokinetics, SC = subcutaneous
Source: Reviewer's analysis of data submitted in Module 5.3.1.2 Study 204958

***Multiple-dose PK in asthma patients***

In two Actual Use studies evaluating the correct use of the AI (Study 204959) or SSD (Study 205667) in subjects with severe eosinophilic asthma, mepolizumab plasma trough concentrations were collected throughout the 12-week treatment period. In subjects with severe eosinophilic asthma, mepolizumab 100-mg SC administered every 4 weeks for 12 weeks using AI or SSD, showed consistent mepolizumab plasma $C_{trough}$ (see Table 13). Furthermore, the observed values of $C_{trough}$ were consistent with the reported $C_{trough}$ values for the lyophilized drug product (refer to clinical pharmacology review BLA 125526 by Dr. Yunzhao Ren dated July 5, 2015, in DARRTS).

**Table 13. Summary of Mepolizumab Plasma Trough Concentrations Postbaseline by Baseline Mepolizumab Use in Actual Use Studies 204959 and 205667 (PK Population)**

| | Mepolizumab Plasma Trough Concentrations (ng/mL) | | | | | |
|---|---|---|---|---|---|---|
| | Week 4 | | Week 8 | | Week 12 | |
| Baseline mepolizumab use | No | Yes | No | Yes | No | Yes |
| 204959 (autoinjector) | n=70 | n=84 | n=73 | n=81 | n=73 | n=84 |
| | 5502.31 (5000.28, 6004.35) | 9447.97 (8624.86, 10271.09) | 8209.82 (7471.11, 8948.53) | 9958.42 (8960.21, 10956.62) | 9854.96 (8893.48, 10816.44) | 11896.44 (10818.91, 12973.97) |
| 205667 (safety syringe) | n=33 | n=22 | n=33 | n=23 | n=32 | n=23 |
| | 6039.90 (4989.12, 7090.67) | 11351.61 (9609.05, 13094.17) | 8158.14 (6680.64, 9635.63) | 10798.60 (9215.71, 12381.48) | 9848.89 (8032.87, 11664.92) | 10710.80 (9082.11, 12339.48) |

Mean with 95% CI presented
PK = pharmacokinetics, CI = confidence interval
Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Page 20

**How do the PB-Eos levels compare between the proposed liquid drug products and the lyophilized product?**

***Single-dose PD in healthy subjects***

PB-Eos counts were measured in the healthy subject PK comparability Study 204958. PB-Eos counts were performed as part of the hematology panel in laboratory assessment. Across the treatment groups (i.e., lyophilized, AI or SSD), a single SC dose of mepolizumab 100 mg decreased PB-Eos counts from a geometric mean baseline ranging from 102 to 119 cells/µL to values at Day 29 of 37 to 38 cells/µL. Reductions at Day 29 from baseline were similar across the three treatment groups, ranging from 66% to 69% (see Figure 6).

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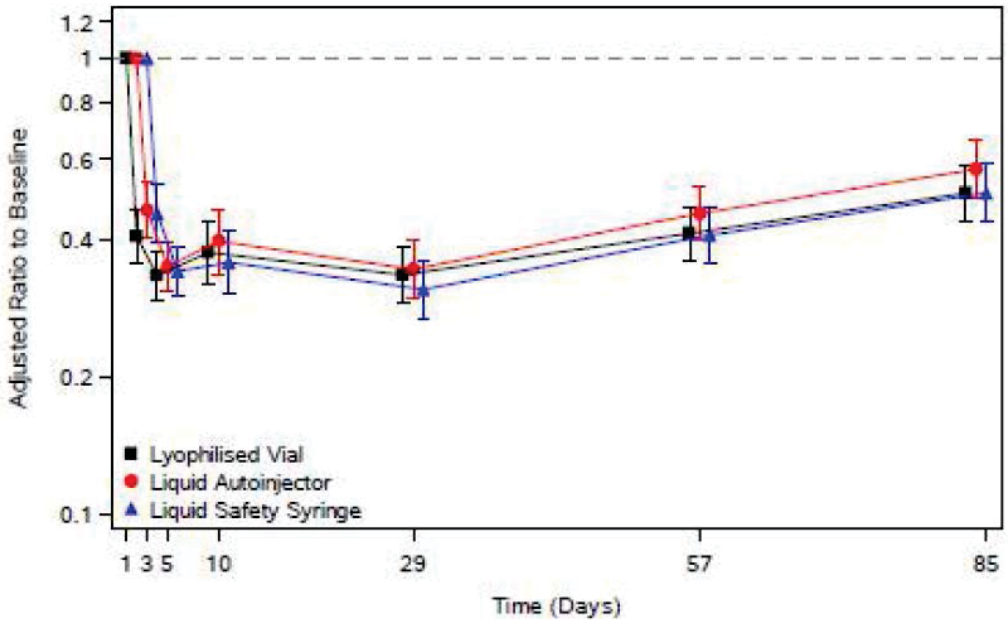
**Figure 6. Adjusted Geometric Mean (95% CI) Ratio to Baseline Blood Eosinophils (109/L) by Visit**




The estimates of the geometric mean are adjusted for baseline blood eosinophil count ($log_e$ scale), injection site (arm, abdomen, thigh) and baseline weight ($log_e$ scale)
Source: Module 5.3.1.2 Study report 204958, page 74

***Multiple-dose PD in asthma patients:***

In two Actual Use studies evaluating the correct use of the AI and SSD by subjects with severe eosinophilic asthma, PB-Eos counts were measured throughout the 12-week treatment period. Administration of mepolizumab liquid drug product every 4 weeks reduced PB-Eos counts consistently across the different time-points and studies, irrespective of whether subjects were receiving mepolizumab at screening. At Week 12, subjects not receiving mepolizumab at screening had reductions in blood eosinophils from baseline of 81% and 84% (Studies 204959 and 205667, respectively) (see Table 14). The PB-Eos reduction from baseline achieved in these two studies mimic the reduction observed with the lyophilized drug product (refer to clinical pharmacology review BLA 125526 by Dr. Yunzhao Ren dated July 5, 2015, in DARRTS).

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**Table 14. Summary of Blood Eosinophil Counts by Baseline Mepolizumab Use in Actual Use Studies 204959 and 205667 (PD Population)**

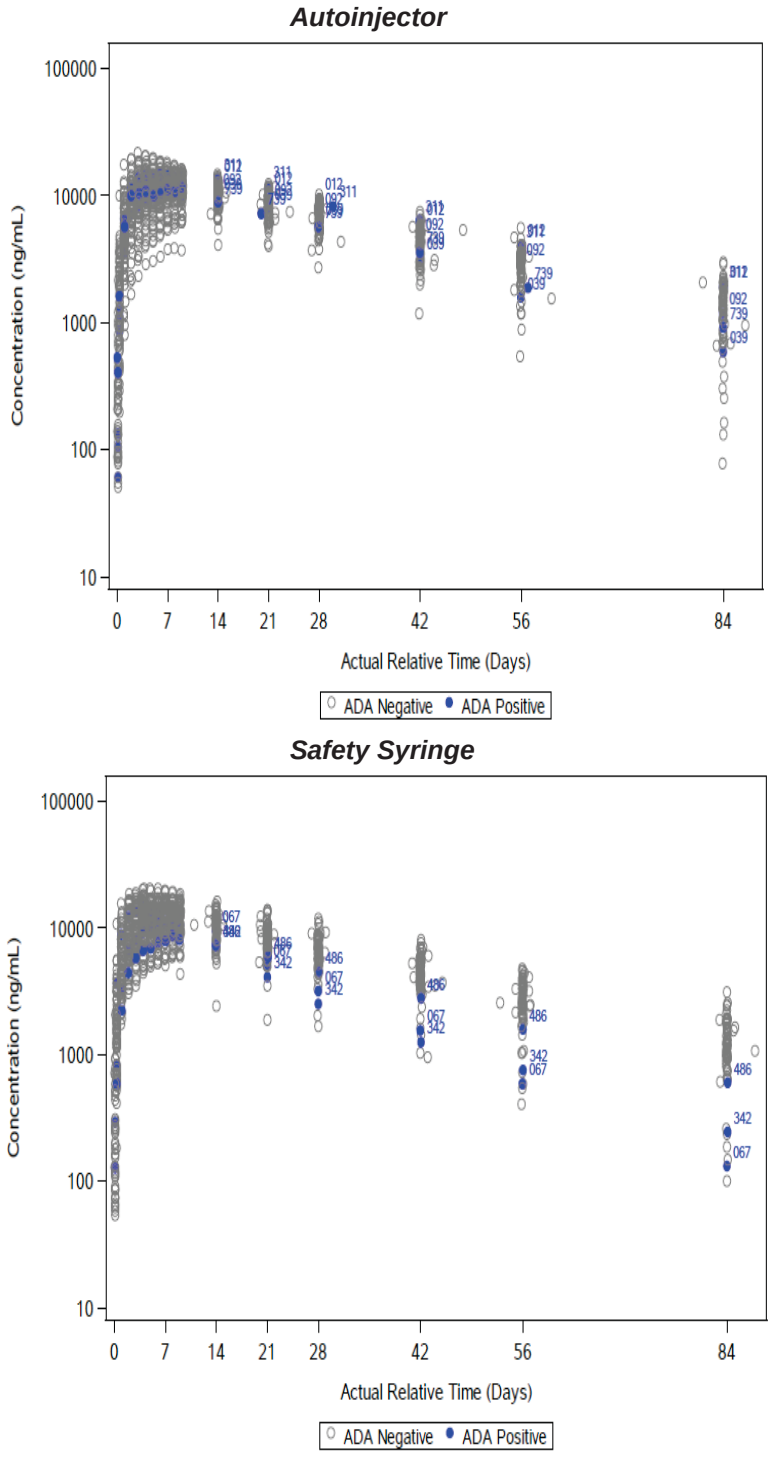
| | Blood Eosinophil Count (GI/L) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Baseline | | Week 4 | | Week 8 | | Week 12 | |
| Baseline mepolizumab use | No | Yes | No | Yes | No | Yes | No | Yes |
| 204959 (autoinjector) | n=74 | n=84 | n=71 | n=82 | n=72 | n=82 | n=67 | n=81 |
| | 0.275 (0.216,0.351) | 0.057 (0.048,0.069) | 0.061 (0.049,0.077) | 0.053 (0.045,0.064) | 0.058 (0.047,0.072) | 0.051 (0.042,0.063) | 0.051 (0.041,0.063) | 0.047 (0.039,0.057) |
| 205667 (safety syringe) | n=33 | n=23 | n=30 | n=22 | n=32 | n=23 | n=29 | n=23 |
| | 0.193 (0.125,0.299) | 0.054 (0.038,0.075) | 0.047 (0.032,0.068) | 0.057 (0.042,0.079) | 0.037 (0.026,0.052) | 0.045 (0.031,0.065) | 0.034 (0.023,0.050) | 0.048 (0.036,0.066) |

Geometric mean with 95% confidence intervals presented
PD = pharmacodynamics
Source: Module 2.7.2. Summary of Clinical Pharmacology Studies, Page 24

**Are the immunogenicity incidences from the clinical studies using autoinjector or safety syringe comparable to the lyophilized product?**

Immunogenicity was evaluated in the three clinical studies with liquid formulation of mepolizumab administered via an autoinjector or safety syringe. Consistent with previous immunogenicity observations during the clinical development program of the lyophilized drug product (≤6%), the incidence of subjects testing positive for anti-mepolizumab antibodies at any visit postbaseline was 5% in healthy subjects (Study 204958), and 1% (Study 204959) and 4% (Study 205667) in severe eosinophilic asthma subjects. Anti-mepolizumab antibodies did not appear to have a significant impact the PK of mepolizumab in Study 204958 (see Figure 7).

**Figure 7. Mepolizumab Concentration-Time in Study 204958 for Autoinjector and Safety Syringe by Anti-Drug Antibody Status**




Source: Module 5.3.1.2 Study report 204958, page 399-400

**Are the bioanalytical methods properly validated to measure PK in plasma samples?**

***Mepolizumab assay***

The concentrations of mepolizumab in human plasma were determined by an antibody capture sandwich ELISA. The measurement of mepolizumab plasma concentrations for both initial lyophilized and proposed new liquid formulation was carried out using the same validated bioanalytical immunoassay method with a Lower Limit of Quantification (LLOQ) of 50 ng/mL. Bioanalytical method validation was reviewed in the original BLA application (refer to clinical pharmacology review BLA 125526 by Dr. Yunzhao Ren dated July 5, 2015, in DARRTS) (see Table 15).

The ISR analysis (conducted for 6% of the samples) in Study 24958 showed that 99.6% of the reassayed samples were within 30% of the corresponding original values demonstrating an acceptable reproducibility of the ELISA method. All samples were analyzed within the demonstrated storage stability parameters established by (b) (4), namely, for up to 8 freeze/thaw cycles and 51 months at −20ºC. Precision and accuracy of the assay in the clinical studies are shown in Table 16 and met the acceptance criteria in FDA Bioanalytical Method Validation Guidance.

***Anti-mepolizumab antibody and neutralizing antibody assay***

The detection of ADA and neutralizing antibody (NAb) against mepolizumab in serum to support the clinical development of both the initial lyophilized and proposed new liquid formulation was carried out using the same validated ADA method (for screening, confirmation, and titer analyses). The presence of ADA and NAb in human serum was determined by using a validated ligand binding assay performed on the Meso Scale Discovery platform. The presence of NAbs in human serum was determined by using a validated indirect competitive ligand binding assay. A summary of the validation data is presented in Table 15. Refer to the Office of Biotechnology Products review for more detailed information regarding assay validation and analysis of clinical study samples.

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**Table 15. Bioanalytical Methods Summary**

| **Mepolizumab assay** | | | |
|---|---|---|---|
| **Validation Report** | **Clinical Studies Supported** | **Summary of Method Description and Validation Parameters** | |
| Validation of an ELISA Method for the Quantification of SB-240563 in Heparin Human Plasma (Assay range 50 – 5000 ng/mL)<br><br>Report numbers 2012N133378_02 (October 2014)<br>2015N263226_00 (November 2015)<br>2017N321052_00 (April 2017)<br>2017N342098_00 (September 2017) | 204958<br>204959<br>205667 | Human plasma samples are diluted 10-fold in assay buffer (Tris, Tween, Bovine serum albumin (TTB) buffer). Mepolizumab is captured with a neutralising idiotypic antibody specific for the binding portion of the drug passively adsorbed to a polystyrene microtiter plate and detected by an Fc specific mouse anti-human IgG1 antibody labelled with horseradish peroxidase allowing for a chemiluminescent response. | |
| | | LLOQ | 50 ng/mL using 100 µL 10-fold diluted plasma |
| | | Validated Range | 50 to 5000 ng/mL |
| | | Within-run Precision (%CV) | ≤10.6% |
| | | Between-run Precision (%CV) | ≤8.1% |
| | | Within-run Accuracy (%Bias) | -15.0 ≤ Bias ≤5.4% |
| | | Between-run Accuracy (%Bias) | -5.6 ≤ Bias ≤-1.1% |
| | | Dilution Integrity | Linearity up to 3,750,000 ng/mL |
| | | Prozone Effect | Not observed at 3,750,000 ng/mL SB-240563 in human plasma |
| | | Stability in Human Plasma and Whole Blood | Room temperature (RT) stability confirmed for at least 24 h. Freeze thaw (FT) stability confirmed for up to eight FT cycles (from -80°C to RT and -20°C to RT). Long term stability at -20°C confirmed for up to 51 months at -20°C and 8 months at -80°C. Whole blood stability at RT or 4°C for 24 h and 37°C for 4 h. |
| | | Processed Sample Stability | Confirmed for samples diluted 1:0 in TTB buffer at 4°C for 24 hours |
| | | Selectivity | No significant matrix effect was observed in six different lots of human plasma after a 1:10 dilution in TTB buffer. No significant interference effect was observed in hemolysed or lipemic plasma. |
| | | Tolerance to non-neutralising ADA | Tolerance observed for all non-neutralising ADA samples examined (≤ 128 titre) |
| | | Tolerance to neutralising ADA | No tolerance observed in neutralising ADA samples examined (n=2) |
| **Anti-Drug Antibody and Neutralising Antibody assays** | | | |
| **Validation Report** | **Clinical Studies Supported** | **Summary of Method Description and Validation Parameters** | |
| Validation Report of an Electrochemiluminescent Immunoassay Method for the Detection of Anti-SB240563 (Mepolizumab) Antibodies in Human Serum Using the Meso-Scale Discovery Platform (6th Generation Assay)<br><br>Report number 2012N137701_00 (12Jul2012) | | Serum samples were diluted with assay diluent, and then incubated with an anti-IL5 blocking antibody. Next, the sample was incubated with biotin-drug and ruthenium-drug conjugates, and transferred to a streptavidin coated MSD plate. The drug conjugate antibody complex was detected with electro chemiluminescence. | |
| | | Screening Cut Point | 1.15 RECL (3x50, normal individuals)<br>1.14 RECL (3x50, diseased individuals) |
| | | Confirmation Cut Point | 49.75% Inhibition (3x20 normal individuals with 7.5 ng/mL PC) |
| | | Within-run Precision (%CV) | ≤7.4% |
| | | Between-run Precision (%CV) | ≤8.8% |
| | | Drug Interference | 250 ng/mL PC screened positive with 100 µg/mL drug |
| | | Sensitivity | 1.03 ng/mL PC |
| | | Sample Dilution (before conjugates) | 1:20 in Assay Diluent or Confirmation Buffer |
| | | Positive Control | Purified rabbit poly clonal, anti-idiotype |
| | | Stability in Human Serum | PC in serum at room temperature (RT) for at least 22 h, refrigerator stability (2-8°C) for up to 7 days, six freeze thaw cycles (from -70°C to RT). Long term stability at -70°C confirmed for up to 688 days. |
| | | Matrix Interference | 20/20 individuals recovered 7.5 ng/mL PC as positive. |

**Table 15. Bioanalytical Methods Summary (cont'd)**

| Anti-Drug Antibody and Neutralising Antibody assays | | | |
|---|---|---|---|
| **Validation Report** | **Clinical Studies Supported** | **Summary of Method Description and Validation Parameters** | |
| Partial Validation of an Electrochemiluminescent Assay for the Detection of anti-SB240563 Antibodies in Human Serum Samples Using the Meso Scale Discovery Platform<br><br>Report number 2018N366495_00 (19Dec2012), Amendment 1: 2018N366496_00, Amendment 2: 2018N366497_00 | 204958<br>204959<br>205667 | Serum samples were diluted with assay diluent, and then incubated with an anti-IL5 blocking antibody. Next, the sample was incubated with biotin-drug and ruthenium-drug conjugates, and transferred to a streptavidin coated MSD plate. The drug conjugate antibody complex was detected with electro chemiluminescence. | |
| | | Screening Cut Point | 1.10 RECL (3x 50, normal individuals) |
| | | Confirmation Cut Point | 43.18% Inhibition (3x 20 normal individuals with 7.5 ng/mL PC) |
| | | Within-run Precision (%CV) | ≤18.7% |
| | | Between-run Precision (%CV) | ≤12.2% |
| | | Drug Interference | 250 ng/mL PC screening positive with 100 µg/mL drug |
| | | Sensitivity | 0.40 ng/mL PC |
| | | Sample Dilution (before conjugates) | 1:20 in Assay Diluent or Confirmation Buffer |
| | | Positive Control | Purified rabbit poly clonal, anti-idiotype |
| | | Stability in Whole Blood | Whole blood stability at RT or 4°C for 24 h |
| Validation Report of a Ligand-Binding Assay for the Detection of Neutralising Antibodies Against SB-240563 in Human Serum Samples | 204958<br>204959<br>205667 | Serum samples were diluted with assay diluent, and then incubated with drug and then biotinylated IL5. Samples were placed into Streptavidin coated wells of on a Meso Scale Discovery plate, and the presence of captured drug was detected with ruthenium labelled mouse anti-human IgG1 antibody. The drug complex was detected with electro chemiluminescence. | |
| | | Screening Cut Point | 77.14% Response (3x 40 normal individuals)<br>78.85% Response (3x 40 asthmatic individuals) |
| | | Within-run Precision (%CV) | ≤11.3% |
| | | Between-run Precision (%CV) | ≤16.4% |
| Report number CD2010-00319--00 (23Sep2010) | | Drug Interference | At 1 µg/mL drug, the PC at the cut point would be 3.5 µg/mL |
| | | Cross Reactivity | Ten normal individuals with non-specific humanized IgG1 was <10% difference from Back Ground Control. |
| | | Free IL-5 Interference | No interference at 20, 200, or 2000 pg/mL |
| | | Sensitivity | 0.40 µg/mL PC |
| | | Positive Control | Purified rabbit poly clonal, anti-idiotype |

Source: Module 2.7.1. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Page 25-28

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**Table 16. Between-Run Accuracy and Precision of Quality Control Samples**

| Study (Report No.) | | Nominal QC Sample Concentrations (ng/mL) | | |
|---|---|---|---|---|
| 204958 (2018N358196_00) | | QC 150 | QC 2000 | QC 4000 |
| | Overall Mean (ng/mL) | 153.9 | 2057.0 | 4118.7 |
| | SD (within-run means) | 10.6 | 101.3 | 148.3 |
| | Precision (%CV) | 6.9 | 4.9 | 3.6 |
| | Average Bias (%) | 2.6 | 2.9 | 3.0 |
| | n | 318 | 321 | 324 |
| 204959 (2018N358198_00) | | QC 150 | QC 2000 | QC 4000 |
| | Overall Mean (ng/mL) | 154.4 | 2069.7 | 4152.6 |
| | SD (within-run means) | 8.7 | 74.9 | 137.9 |
| | Precision (%CV) | 5.6 | 3.6 | 3.3 |
| | Average Bias (%) | 2.9 | 3.5 | 3.8 |
| | n | 53 | 56 | 56 |
| 205667 (2018N356818_00) | | QC 150 | QC 2000 | QC 4000 |
| | Overall Mean (ng/mL) | 154.0 | 2083.7 | 4058.9 |
| | SD (within-run means) | 11.9 | 84.5 | 222.7 |
| | Precision (%CV) | 7.7 | 4.1 | 5.5 |
| | Average Bias (%) | 2.7 | 4.2 | 1.5 |
| | n | 20 | 19 | 20 |

QC = quality control
Source: Module 2.7.1. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Page 29

# 7 Sources of Clinical Data and Review Strategy

## 7.1. Table of Clinical Studies

A listing of the clinical studies in this submission is shown in Table 17. The Applicant conducted a single-dose, clinical pharmacology PK/BE study (204958) in healthy volunteers to compare the PK of the proposed Nucala injection prefilled AI and SSD with the approved reference product, Nucala for injection lyophilized powder from a vial, and two actual use studies (204959 and 205667) for Nucala injection prefilled AI and SSD in patients with severe eosinophilic asthma.

(b) (4)

[redacted]

**Table 17. Listing of Clinical Studies Relevant to BLA 761122**

| Study Identifier (Identifier of Study Report) | Study Objective(s) | Study Design | Healthy Subjects or Diagnosis of Patients | Treatment Details (Test Product(s); Dosage Regimen; Route; Duration) | Total No. of Subjects by Group Entered/ Completed | Study Reporting Status (Type of Report) |
|---|---|---|---|---|---|---|
| Pharmacokinetic/Pharmacodynamic Studies | | | | | | |
| 204958 (2017N342446_01) | PK/PD<br>Safety and Tolerability<br>Immunogenicity<br>Safety syringe and autoinjector use | R, OL, PG | Healthy subjects | Mepolizumab 100 mg SC liquid drug product, single dose either in autoinjector or safety syringe<br>Mepolizumab 100 mg SC lyophilised powder for solution for injection, single dose. | Autoinjector 79/79<br><br>Safety syringe 80/80<br><br>Lyophilised powder 85/84 | Completed/ Reported (CPSR) |
| Efficacy and Safety Studies: Controlled Clinical Studies Using Liquid | | | | | | |
| (b) (4) [redacted] | | | | | | |
| Real World Use and Safety Studies: Uncontrolled Clinical Studies | | | | | | |
| 204959 (2017N349209_00) | Autoinjector use<br>PK/PD<br>Asthma exacerbations<br>Safety and Tolerability<br>Immunogenicity | OL, RWU | Severe eosinophilic asthma | Mepolizumab 100 mg SC liquid drug product Q4W for 12 weeks self-administered by the subject (or their caregiver) using an autoinjector. | 159/157[a] | Completed/ Reported (CSR) |
| 205667 (2017N331753_00) | Safety syringe use<br>PK/PD<br>Asthma exacerbations<br>Safety and Tolerability<br>Immunogenicity | OL, RWU | Severe eosinophilic asthma | Mepolizumab 100 mg SC liquid drug product Q4W for 12 weeks self-administered by the subject (or their caregiver) using a safety syringe. | 56/55 | Completed/ Reported (CSR) |

Source: M5.2 Tabular Listing of All Clinical Studies

## 7.2. Review Strategy

The efficacy review is based upon establishing PK bioequivalence between the reference lyophilized product and the proposed prefilled AI and SSD. A detailed review of clinical pharmacology study 204958 and additional clinical pharmacology data can be found in Section 6 Clinical Pharmacology. The safety review focuses on data from the actual use studies and the clinical pharmacology study for the proposed Nucala injection prefilled autoinjector and safety syringe. The protocols and study reports are summarized and reviewed in Section 8.1 Review of Relevant Individual Trials Used to Support Efficacy and Safety.

A statement of compliance with good clinical practices is located in each complete study report. The study protocol, amendments, informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational center ethics committee or institutional review board, in accordance with the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, good clinical practices, and applicable country-specific requirements, including United States of America 21 CFR 312.3(b) for constitution of independent ethics committees.

A financial disclosure checklist is attached in the appendix of this review. As each investigator contributed only a limited number of subjects for each study, the overall contribution of each site to the totality of the data from this program is small. Any potential for improper conduct at each site would be unlikely to affect the outcomes of clinical studies in this BLA (761122).

# 8 Statistical and Clinical and Evaluation

## 8.1. Review of Relevant Individual Trials Used to Support Efficacy and Safety

### 8.1.1. Study 204958

**Title:** An open-label, randomized, three-arm, single-dose, multicenter, parallel-group study in healthy subjects to compare the pharmacokinetics of subcutaneous mepolizumab when delivered as a liquid drug product in a safety syringe or an autoinjector with a reconstituted lyophilized drug product from a vial.

Study period: January 6 – August 11, 2017
Final report: July 17, 2018

**Protocol Amendments**

The study protocol was approved on August 31, 2015, with three amendments on November 5, 2016; November 17, 2016; and July 10, 2017, respectively. The three amendments involved editorial changes for abbreviations, updated Applicant/medical monitor contact information forms, minor changes in descriptions of subject withdrawal and follow-up and regulatory reporting requirements for SAEs, and removal of study procedures to capture cardiovascular events and death because this was a single-dose study in healthy population. These protocol amendments are unlikely to have impacted study results.

**Results**

The study design and PK/immunogenicity results are described above in Section 6. Therefore, only the safety findings are presented in this section.

*Safety*

Overall, 82 (34%) subjects reported any AE. The incidence of AEs was similar across the three treatment groups. Headache (9%), viral upper respiratory tract infection (URTI) (5%), and fatigue (3%) were the AEs reported by ≥3% of subjects in either the total liquid or lyophilized drug product treatment groups. Other reported AEs included back pain, diarrhea, and dizziness. AEs considered to be drug-related by the investigator were reported in 54 (22%) subjects, and there were no subjects with AEs that led to withdrawal from the study. One subject in lyophilized drug (reference) group reported a post-treatment (>28 days after dosing) SAE of atrial fibrillation that was considered not related to study treatment by the investigator and resolved. No other SAE (fatal or non-fatal) was reported during the study. The study did not reveal new safety signals.

**Table 18. Adverse Events Reported in ≥3% Subjects in Any Study Group**

| | Number (%) of Subjects | | | | |
|---|---|---|---|---|---|
| | Mepolizumab 100 mg SC | | | | |
| | Lyophilised Vial (N=85) | Liquid Drug Product In Autoinjector (N=79) | Liquid Drug Product In Safety Syringe (N=80) | Total Liquid (N=159) | Total (N=244) |
| **Any AE** | **25 (29)** | **27 (34)** | **30 (38)** | **57 (36)** | **82 (34)** |
| Headache | 6 (7) | 9 (11) | 8 (10) | 17 (11) | 23 (9) |
| Viral upper respiratory tract infection | 2 (2) | 3 (4) | 6 (8) | 9 (6) | 11 (5) |
| Fatigue | 5 (6) | 2 (3) | 1 (1) | 3 (2) | 8 (3) |

Source: M5.3.1 Reports of Biopharmaceutic Studies, (Study) 204958, Page 56

### 8.1.2. Study 204959

**Title:** An open-label, single-arm, repeat-dose, multicenter study to evaluate the use of an autoinjector for the subcutaneous administration of mepolizumab in subjects with severe eosinophilic asthma.

Study period: May 4 – November 30, 2017
Final report: May 22, 2018

**Protocol Amendments**

The study protocol was approved on August 18, 2016, with two amendments on October 13, 2016, and February 15, 2017, respectively. The first amendment included editorial changes for the study objectives from the descriptive to tabular format, refining descriptions of inclusion and exclusion criteria and assessment of autoinjector use, and removed references cited in the protocol. The second amendment included an explanation of autoinjector label with and without a pictogram; an increased subject number that would be screened (150 to 225) and enrolled (105 to 158) based on the estimated proportion of subjects who would successfully self-administer the

mepolizumab doses (no sample size calculation was performed); refined descriptions of hypotheses, inclusion criteria, permitted medications, and non-drug therapy, and benefit assessment; removal of the subjects' practice by injection into a foam pad; and other editorial changes. These protocol amendments are unlikely to have significantly impacted the study results or safety assessments.

**Trial Design**

This was an open-label, single-arm, repeat-dose, multicenter study to evaluate the use of mepolizumab liquid drug product in an autoinjector for the self-administration by subjects (or their caregivers) with severe eosinophilic asthma.

The primary objective of this study was to assess the use of the mepolizumab liquid drug product in an AI for self-administration by subjects with severe eosinophilic asthma. The secondary objective of this study was to assess the use of mepolizumab liquid drug product in an AI outside the clinic setting. The safety objective of this study was to evaluate the safety and tolerability of mepolizumab liquid drug product in an AI.

Key Inclusion / Exclusion Criteria:

- Age ≥ 12 years of age
- Asthma diagnosis for ≥2 years per National Heart, Lung, and Blood Institute guidelines or Global Initiative for Asthma guidelines
- Either no mepolizumab treatment at Visit 1 or 12 weeks of stable 100 mg Q4 week mepolizumab treatment prior to Visit 1
- For those not already receiving mepolizumab treatment:
    - Eosinophilic asthma defined as peripheral blood eosinophil count of ≥150 cells/μL at Visit 1 or ≥300 cells/μL in the 12 months prior to Visit 1
    - Well-documented need for high-dose ICS in the 12 months prior to Visit 1 (with or without maintenance oral corticosteroids)
    - Need for (or documented failure with) additional controller medication besides high-dose ICS in the past 12 months for at least 3 successive months
    - Confirmed history of one or more asthma exacerbations requiring treatment with systemic corticosteroid in the 12 months prior to visit 1.

Treatments

Mepolizumab liquid drug product was supplied by GSK in glass syringes with staked needles (½ inch x 29-gauge thin-wall), sealed with latex-free rubber plungers. These were assembled in single-use, disposable autoinjectors to enable automatic delivery of the drug product. Each device delivered 100-mg mepolizumab in 1.0-mL solution.

Eligible subjects received 100-mg SC mepolizumab liquid drug product in an autoinjector self-administered in the thigh or abdomen, or in the upper arm by a caregiver once every 4 weeks.

The first and third doses of mepolizumab were self-administered in-clinic under observation, and the second dose was self-administered unobserved outside the clinic (at home).

For the purposes of this study, "self-administration" is defined as the administration by either the subject themselves or by their caregiver. When the subject chose to have a caregiver perform the injection, the same caregiver injected all doses. For the first dose (Week 0), subjects/caregivers were provided with in-clinic training (a walk-through of the IFU). For the second dose (Week 4), subjects/caregivers did not have any in-clinic training; they had the IFU for support but could request further guidance via telephone or an unscheduled clinic visit (guidance involved the review of the IFU and/or answering of questions related to the IFU). For the third dose (Week 8), subjects/caregivers did not have further training or guidance though they had the IFU for support. Subjects attended a total of three on-treatment study visits and an end-of-study visit approximately 4 weeks after the final dose. At the end of study, subjects were asked to record their overall experience on treatment and the use of the autoinjector.

In this single-arm study, two different device labels were used based on guidance provided by regulatory agencies regarding device labeling preferences. One had standard labeling elements and a pictogram (i.e., quick reference guide), hereafter referred to as "standard device label + pictogram autoinjector," and was used at sites in the United States, United Kingdom, and Australia. The other had only the standard labeling elements without a pictogram, hereafter referred to as "standard device label autoinjector," and used at sites in Germany, Canada, Russia, and Sweden.

At the first and third doses of mepolizumab, the investigator or designee observed, using a checklist based on the autoinjector IFU, the ability of the subject/caregiver to (self-)administer the injection. The second dose was self-administered unobserved outside of the clinic (at home). The observer checklist was used to determine if each step, according to the IFU, was completed easily, with some difficulty, or not completed/intervention required. Any user errors or device malfunctions were recorded and reported using the Autoinjector (Pen) Error/Failure Reporting Form. At Week 4, when self-administration was performed outside the clinic (within 24 hours of attending the visit 3 clinic visit), the subject/caregiver recorded the date, time, and site of injection, who administered the injection (subject or caregiver), and completed a checklist similar to the observer checklist outlining various steps in the IFU and whether each step was completed easily, with some difficulty, or not completed.

Responses on the checklist were checked by the investigator or designee at the next clinic visit. Failure to perform one of the critical steps was deemed a failure to successfully administer the injection. All devices utilized as part of the study were returned to the clinic and assessed to confirm that the device had been successfully actuated. Unsuccessful injections underwent a root-cause investigation and evaluation to assess whether any were associated with the instructions/use of the device or whether it was associated with a device failure using the Autoinjector (Pen) Error/Failure Reporting Form. All devices were evaluated by Device Engineering, post-use, to assess overall performance and robustness of the device.

Following each injection, any pain at the injection site was assessed by the subject using a visual analog scale (VAS) immediately after injection, 1 hour after injection, and 24 hours (±4 hours) after injection. The results were recorded in the patient diary. A short survey was administered to all subjects at the end-of-study/early withdrawal visit.

**Results**

There were 179 subjects screened and 159 subjects were enrolled in the study (104 subjects using the standard device label + pictogram autoinjector and 55 subjects using the standard device label autoinjector). Demographics of the study subjects are shown in Table 19. Most subjects were white (80%) females (62%), with a mean BMI of 31 kg/m2 and a mean age of 49 years. There were 11 adolescents (12 to 17 years) and 26 elderly subjects (≥65 years) in this study. Primary language spoken was not captured.

**Table 19. Subject Demographics, Study 204959**

| | Mepolizumab Liquid Autoinjector (N=159) |
|---|---|
| Gender, n (%) | |
| Female | 98 (62) |
| Male | 61 (38) |
| Age [1] (years) | |
| Mean (SD) | 49.3 (16.18) |
| Min, Max | 12, 77 |
| Age Group [1] (years), n (%) | |
| Adolescent (12 to 17) | 11 (7) |
| Adult (18 to 64) | 122 (77) |
| Elderly (≥65) | 26 (16) |
| BMI (kg/m$^2$) [2] | |
| Mean (SD) | 31.39 (7.606) |
| Ethnicity, n (%) | |
| Hispanic or Latino | 11 (7) |
| Not Hispanic or Latino | 148 (93) |
| Race Detail, n (%) | |
| White - White/Caucasian/European Heritage | 126 (79) |
| African American/African Heritage | 25 (16) |
| Asian - South East Asian Heritage | 3 (2) |
| Asian - Central/South Asian Heritage | 2 (1) |
| Asian - East Asian Heritage | 1 (<1) |
| White - Arabic/North African Heritage | 1 (<1) |
| Other [3] | 1 (<1) |

Source: M5.3.5 Reports of Efficacy and Safety studies, (Study) 204959, Page 47

Of the 159 subjects who commenced the treatment period, all subjects (or their caregivers) attempted to self-administer at least one dose of study treatment and successfully self-administered at least one dose. All but two subjects (99%) completed the study. One subject discontinued study treatment on study Day 1 after the first dose for the primary reason of "physician decision" ("non-compliant with study procedures" and "withdrawn due to unreliability"). The other subject was withdrawn from the study after the first dose for the primary reason of adverse event related to a road traffic accident.

**Table 20. Subject Disposition, Study 204959**

| Treatment Status<br>Reason [1]<br>Sub-reason [2] | Number of Subjects, n (%)<br>Mepolizumab Liquid Autoinjector (N=159) |
|---|---|
| Completed | 157 (99) |
| Permanently Discontinued Study Treatment | 2 (1) |
| AE | 1 (<1) |
| Physician Decision | 1 (<1) |
| Patient Non-Compliant with Study Procedures. Withdrawn Due to Unreliability. | 1 (<1) |
| Withdrawn from the Study | 2 (1) |
| AE | 1 (<1) |
| Physician Decision | 1 (<1) |
| Failure to Comply with Study Procedures and Unreliability. | 1 (<1) |

Source: M5.3.5 Reports of Efficacy and Safety Studies, (Study) 204959, Page 46

The primary endpoint of this study was the proportion of subjects/caregivers who successfully self-administered the third dose of mepolizumab liquid drug product using an autoinjector when observed in-clinic at Week 8. All but one subject in both groups (those using the standard device label + pictogram autoinjector and those using the standard device label autoinjector only) who attempted an injection were reported by the investigator/site staff to have successfully self-administered the third dose of mepolizumab at Week 8 when observed in the clinic (see Table 21 and Table 22).

The secondary endpoint of this study was the proportion of subjects/caregivers who successfully self-administered the second dose of mepolizumab liquid drug product using an autoinjector when unobserved at home at Week 4. All but two subjects in both groups (those using the standard device label + pictogram autoinjector and those using the standard device label autoinjector only) who attempted an injection were reported to have successfully self-administered the second dose of mepolizumab at Week 4 when unobserved at home.

There were no differences in proportion of successfully self-administered mepolizumab autoinjector between subjects using the standard device label + pictogram and using the standard device label only.

**Table 21. Proportion of Subjects Successfully Self-Administered Mepolizumab Liquid Autoinjector by Visit, Standard Device Label + Pictogram**

| Visit | Mepolizumab Liquid Autoinjector (Standard Device Label + Pictogram Autoinjector) (N=104) | | | |
|---|---|---|---|---|
| | Attempted Injections, n | Successful Injections, n (%) [a,b] [95% CI] | Unsuccessful Injections [b], n (%) | Reason, n |
| Week 0, First Dose (observed in-clinic) | 104 | 101 (97) [92, 99] | 3 (3) | Incorrect Injection Site (Upper Arm) – 2 [c]<br>Pen Pulled Away Before End of Injection – 1 [d, e]<br>Evidence of Liquid Leaking from Injection Site -1 [d, e] |
| Week 4, Second Dose (unobserved at home) | 103 | 101 (98) [93, 100] | 2 (2) | Incorrect Injection Site (Upper Arm) – 1 [c]<br>Other User Error -1 [d, f]<br>Reported Device Failure (Other) – 1<br>Unsubstantiated following root-cause analysis – 1 [d, f] |
| **Week 8, Third Dose Primary Endpoint** (observed in-clinic) | 103 | 102 (99) [95, 100] | 1 (<1) | Incorrect Injection Site (Upper Arm) – 1 [c] |
| Weeks 4 and 8 | 103 | 100 (97) [92, 99] | | |
| Weeks 0, 4, and 8 | 103 | 98 (95) [89, 98] | | |

Source: M5.3.5 Reports of Efficacy and Safety Studies, (Study) 204959, Page 55

**Table 22. Proportion of Subjects Successfully Self-Administered Mepolizumab Liquid Autoinjector by Visit, Standard Device Label**

| Visit | Mepolizumab Liquid Autoinjector (Standard Device Label Autoinjector) (N=55) | | | |
|---|---|---|---|---|
| | Attempted Injections, n | Successful Injections, n (%) [a,b] [95% CI] | Unsuccessful Injections [b], n (%) | Reason, n |
| Week 0, First Dose (observed in-clinic) | 55 | 52 (95) [85, 99] | 3 (5) | Pen Pulled Away Before End of Injection – 2 [c, d]<br>Evidence of Liquid Leaking from Injection Site – 1 [e]<br>Other User Error – 1 [d]<br>Reported Device Failure (Other) – 2<br>Text entered into 'Device Failure' box of eCRF – 1 [d]<br>Unsubstantiated following root-cause analysis – 1[e] |
| Week 4, Second Dose (unobserved at home) | 54 | 52 (96) [87, 100] | 2 (4) | Pen Pulled Away Before End of Injection – 2 [f]<br>Reported Device Failure (Other) – 1<br>Text entered into 'Device Failure' box of eCRF – 1 [f, g] |
| **Week 8, Third Dose Primary Endpoint** (observed in-clinic) | 54 | 53 (98) [90, 100] | 1 (2) | Incorrect Injection Site (Upper Arm) – 1 [f, h] |
| Weeks 4 and 8 | 54 | 51 (94) [85, 99] | | |
| Weeks 0, 4, and 8 | 54 | 48 (89) [77, 96] | | |

Source: M5.3.5 Reports of Efficacy and Safety Studies, (Study) 204959, Page 70

Exit interviews were conducted for 25 subjects who self-administered the injections; 14 used the standard device label autoinjector (six subjects in Canada and eight subjects in Germany) and 11 used the standard device label + pictogram autoinjector (seven subjects in the United States and four subjects in Australia) to assess the subject experience of using the autoinjector to self-administer mepolizumab. All subjects (100%) rated the autoinjector to be "moderately" to "extremely" easy to use, and all subjects reported the autoinjector to be "moderately" to "extremely" convenient. Twenty-three subjects (92%) stated that they were "very satisfied" with the autoinjector.

*Safety*

Overall, 56 (35%) subjects, including 5 out of 11 adolescent subjects enrolled, reported an on-treatment AE. Table 23 shows the AEs reported in ≥3% of subjects. Other AEs included fatigue, ear discomfort, injection site pain (bruising, erythema, hemorrhage), chills, asthenia, dizziness, lethargy, migraine, neuralgia, arthralgia, back (neck) pain, muscle spasm, myalgia, rash, pruritus, diarrhea, dry mouth, gastric ulcer, increased blood glucose, bone fracture, etc.

**Table 23. Adverse Events Reported in ≥3% Subjects, Study 204959**

| Preferred Term | Number of Subjects, n (%)<br>Mepolizumab Liquid Autoinjector (N=159) |
|---|---|
| Any AE | 56 (35) |
| Nasopharyngitis | 9 (6) |
| Headache | 8 (5) |
| Upper respiratory tract infection | 6 (4) |
| Lower respiratory tract infection | 5 (3) |
| Urinary tract infection | 5 (3) |

Source: M5.3.5 Reports of Efficacy and Safety Studies, (Study) 204959, Page 94

No deaths were reported in the study. There were nine non-fatal SAEs (allergic alveolitis, asthma, pneumothorax, chest discomfort, four bone fractures, and road traffic accident) reported during the study. Of the nine SAEs, six were reported by a subject who had a road traffic accident. All SAEs were considered not related to mepolizumab by the investigator. The road traffic accident event and accompanying five SAEs resulted in discontinuation of study treatment and withdrawal of this subject from the study. Although not powered for safety, no new safety signals were observed in this study.

Any pain at the injection site was assessed by the subject using a VAS score from 0 (no pain) to 100 (worst imaginable pain) immediately after injection, at 1 hour and 24 hours after injection. Table 24 shows that subjects reported high VAS scores immediately after the self-injection, and the pain VAS scores dropped at 1 and 24 hours after the self-injection. At the first self-injection (Week 0), subjects reported higher pain VAS scores than at the second (Week 4) and third (Week 8) self-injections.

**Table 24. VAS Pain Scores Immediately, 1 Hour, and 24 Hours After Self-Administration of Mepolizumab Autoinjector, Study 204959**

| Visit<br>Time Following Self-Administration | Mepolizumab Liquid Autoinjector (N=159) | | | |
|---|---|---|---|---|
| | n | Mean (SD) | Median | Min, Max |
| **Week 0, First Dose, n** | 159 | | | |
| Immediately | 141 | 10.5 (17.09) | 3.0 | 0, 70 |
| 1 h | 140 | 3.3 (8.43) | 0.0 | 0, 51 |
| 24 h | 136 | 1.8 (5.79) | 0.0 | 0, 41 |
| **Week 4, Second Dose, n** | 159 | | | |
| Immediately | 129 | 8.4 (16.58) | 2.0 | 0, 100 [a] |
| 1 h | 109 | 3.7 (12.29) | 0.0 | 0, 100 [a] |
| 24 h | 134 | 2.3 (8.08) | 0.0 | 0, 70 |
| **Week 8, Third Dose, n** | 159 | | | |
| Immediately | 150 | 7.3 (16.17) | 0.0 | 0, 100 [a] |
| 1 h | 130 | 2.2 (8.22) | 0.0 | 0, 68 |
| 24 h | 116 | 1.0 (4.46) | 0.0 | 0, 35 |

VAS = visual analogue scale
Source: M5.3.5 Reports of Efficacy and Safety Studies, (Study) 204959, Page 103

In this study, there were no reports of incidents or malfunctions associated with the autoinjector. Exit interviews of subjects using either the standard device label + pictogram autoinjector or the standard device label autoinjector showed the overall positive perceptions of the autoinjector.

Blood samples were collected for detection of binding and neutralizing anti-mepolizumab antibodies prior to dosing at Week 0 and at the end of study. Antibody assays utilized the electrochemiluminescence detection platform. For the anti-drug antibody detection assay, samples with a positive result continued for confirmation analysis. Samples with a positive confirmation analysis were considered positive ADA against mepolizumab. These positive samples were further characterized for degree of binding (a titer value) and whether the antibody response was neutralizing with a NAb assay.

Five subjects tested positive for ADA at any time during this study, none of whom tested positive for NAbs. Of these, four subjects were positive for ADA at baseline and two subjects were positive for ADA at the end-of-study visit. Three subjects with positive ADA test at baseline had negative ADA test at the end-of-study visit. One subject with negative ADA test at baseline had positive ADA test with a titer value of 32. These subjects did not report local injection site reactions or systemic reactions during the study.

One subject with positive ADA test at baseline and at the end-of-study visit had an increase in the ADA titer value from 16 at baseline to 5120 at the end-of-study visit. This 40-year-old female subject had not participated in other mepolizumab clinical trials prior to this study. The reported current medical conditions at baseline were eosinophilic asthma, nasal polyps, sinusitis, and hypercholesterolemia. Only one AE reported for this subject was a non-SAE of injection site

hemorrhage of mild intensity that resolved within 10 days. There was no evidence that the blood eosinophil counts were affected by the presence of ADA in the study.

There were no allergic (type I hypersensitivity) systemic reactions reported in this study.

### 8.1.3. Study 205667

**Title:** An open-label, single-arm, repeat-dose, multicenter study to evaluate the use of a safety syringe for the subcutaneous administration of mepolizumab in subjects with severe eosinophilic asthma.

Study period: February 1, 2017, to August 8, 2017
Final report: January 24, 2018

**Protocol Amendment**

The study protocol was approved on August 18, 2016, with one amendment on October 6, 2016. The amendment involved refinement of the text of study procedures, editorial changes, and removal of references cited in the protocol. The protocol amendment was unlikely to have impacted the study results and subject safety assessment.

**Trial Design**

Except for the use of the SSD presentation rather than AI, this study was identical to study 204959. Thus, readers may refer to Section 8.1.2 for details of the study design.

Mepolizumab liquid drug product was supplied by GSK in glass syringes with staked needles (½ inch x 29-gauge thin-wall), sealed with latex-free rubber plungers. These were assembled in single-use, disposable safety syringes to enable delivery of the drug product. Each safety syringe delivered 100-mg mepolizumab in 1.0-mL solution. The prefilled syringe was filled and assembled at GSK.

**Results**

There were 75 subjects screened and 56 subjects were enrolled in the study. Demographics of the study subjects are shown in Table 25. Most subjects were white (80%) females (59%) with a mean BMI of 31 kg/m2 and a mean age of 51 years. There were two adolescents (12 to 17 years) and seven elderly subjects (≥65 years) in this study.

**Table 25. Subject Demographics, Study 205667**

| | Mepolizumab Liquid Safety Syringe (N=56) |
|---|---|
| Gender, n (%) | |
| Female | 33 (59) |
| Male | 23 (41) |
| Age [1] (years) | |
| Mean (SD) | 50.8 (12.98) |
| Min, Max | 15, 74 |
| Age group [1] (years), n (%) | |
| Adolescent (12 to 17) | 2 (4) |
| Adult (18 to 64) | 47 (84) |
| ≥65 to 84 years | 7 (13) |
| BMI (kg/m$^2$) | |
| Mean (SD) | 31.14 (8.474) |
| Ethnicity, n (%) | |
| Not Hispanic or Latino | 56 (100) |
| Race Detail, n (%) | |
| White - White/Caucasian/European Heritage | 45 (80) |
| African American/African Heritage | 8 (14) |
| White - Arabic/North African Heritage | 2 (4) |
| Asian - Central/South Asian Heritage | 1 (2) |

Source: M5.3.5 Reports of Efficacy and Safety Studies, (Study) 205667, page 43

Of the 56 subjects who commenced the treatment period, all subjects (or their caregivers) attempted to self-administer at least one dose of study treatment, and 55 subjects (98%) completed the study. One subject discontinued the study treatment after the second dose at Week 4 for the adverse events lack of efficacy and asthma that resulted in hospitalization. All subjects (or their caregivers) successfully self-administered mepolizumab in the SSD at each timepoint (see Table 26).

**Table 26. Proportion of Subjects Successfully Self-Administered Mepolizumab Liquid Safety Syringe by Visit**

| | Mepolizumab Liquid Safety Syringe (N=56) | | |
|---|---|---|---|
| | Attempted Injections | Successful Injections [a] | |
| Dose Interval | n (%) | n (%) | 95% CI |
| Week 0, First Dose [b] | 56 (100) | 56 (100) | (94, 100) |
| Week 4, Second Dose [c] | 56 (100) | 56 (100) | (94, 100) |
| **Week 8, Third Dose [b] (primary endpoint)** | 55 (98) | 55 (100) | (94, 100) |
| Weeks 4, Second Dose [c] and 8 [b] | 55 (98) | 55 (100) | (94, 100) |
| Weeks 0, First Dose [c], 4, Second Dose [b], and 8, Third Dose [c] | 55 (98) | 55 (100) | (94, 100) |

Source: M5.3.5 Reports of Efficacy and Safety Studies, (Study) 205667, page 47

*Safety*

Seventeen subjects (30%) reported an adverse event during the study. The most commonly (≥3%) reported AEs were viral URTIs (four subjects, 7%) and asthma (two subjects, 4%) (see Table 27). Other AEs reported by one subject in the study include fatigue, injection site reaction, rhinorrhea, wheezing, acute sinusitis, conjunctivitis, gastroenteritis viral, diverticulitis, psoriasis, rash, tachycardia, diabetes inadequate control, urinary tract infection.

**Table 27. Adverse Events Reported in ≥3% Subjects, Study 205667**

| Preferred Term | Number of Subjects, n (%) Mepolizumab Liquid Safety Syringe (N=56) |
|---|---|
| Any AE | 17 (30) |
| Viral URTI | 4 (7) |
| Asthma | 2 (4) |

AE = adverse event, URTI = upper respiratory tract infection.
Source: M5.3.5 Reports of Efficacy and Safety Studies, (Study) 205667, page 43

There were no deaths reported during the study. There were three non-fatal SAEs reported (two asthma and one diverticulitis). One subject with asthma discontinued the study treatment after the second dose at Week 4 for the adverse events lack of efficacy and asthma that resulted in hospitalization.

The proportion of subjects reporting any pain (VAS score >0) immediately following injection was 64% after the first dose (Week 0), 54% after the second dose (Week 4), and 51% after the third dose (Week 8). Of these subjects, 11% expressed that this pain was greater than expected following the first dose, 5% following the second dose, and 25% following the third dose. The VAS ranged from a score of 0 (no pain) to 100 (worst imaginable pain). Subjects who experienced pain reported the highest amount of pain immediately following the first dose of study treatment at Week 0 (median VAS score of 2.5). At subsequent injections, the amount of pain reported immediately after injection decreased compared with the first dose, 2.0 following the second dose at Week 4, and 1.0 following the third dose at Week 8 (see Table 28).

For each injection, the VAS score was the highest immediately following the injection and decreased by 1 hour and 24 hours post-injection. Subjects expressed that the pain they experienced immediately, 1 hour, and 24 hours after each injection was acceptable except for one subject who reported unacceptable pain 24 hours after the Week 4 (at home) injection. At 1 hour and 24 hours following each injection, the proportion of subjects experiencing pain decreased as did the relative degree of pain reported.

**Table 28. VAS Pain Scores Immediately, 1 Hour, and 24 Hours After Self-Administration of Mepolizumab Safety Syringe, Study 205667**

| Dose Interval Time Following Self-Administration | Mepolizumab Liquid Safety Syringe (N=56) | | | |
|---|---|---|---|---|
| | n | Mean (SD) | Median | Min, Max |
| **Week 0, First Dose, n** | 56 | | | |
| Immediately | 56 | 9.1 (13.93) | 2.5 | 0, 57 |
| 1 h | 51 | 2.2 (5.95) | 0.0 | 0, 27 |
| 24 h | 53 | 1.8 (4.93) | 0.0 | 0, 25 |
| **Week 4, Second Dose, n** | 56 | | | |
| Immediately | 41 | 5.4 (9.96) | 2.0 | 0, 45 |
| 1 h | 42 | 3.5 (11.90) | 0.0 | 0, 70 |
| 24 h | 46 | 2.1 (8.91) | 0.0 | 0, 58 |
| **Week 8, Third Dose, n** | 56 | | | |
| Immediately | 47 | 4.6 (11.57) | 1.0 | 0, 72 |
| 1 h | 47 | 1.1 (2.81) | 0.0 | 0, 13 |
| 24 h | 46 | 0.9 (2.26) | 0.0 | 0, 10 |

VAS = visual analogue scale, SD = standard deviation
Source: M5.3.5 Reports of Efficacy and Safety Studies, (Study) 205667, page 72

No reports of incidents or malfunctions were associated with the safety syringe in the study.

Blood samples were collected for detection of binding and neutralizing anti-mepolizumab antibodies prior to dosing at Week 0 and at the end of study using assays as described in section 8.1.2 for study 204959. Four subjects tested positive for ADAs at any time during this study, none of whom tested positive for NAbs. Of these, three subjects (5%) tested positive for ADA at baseline and two subjects were positive for ADAs at the end-of-study visit. The subject with positive ADAs at baseline and at the end-of-study visit had no change in the ADA titer value of 32. Two subjects with a positive ADAs test at baseline had a negative ADA test at the end-of-study visit. One subject with a negative ADA test at baseline had a positive ADA test with a titer value of 128. These subjects did not report local injection site reactions or systemic reactions during the study.

There were no allergic (type I hypersensitivity) systemic reactions reported in this study.

(b) (4)

[redacted]


#### 8.1.5. Integrated Assessment of Effectiveness

No integrated assessment is necessary as efficacy of the proposed prefilled AI and SSD products was demonstrated by establishing bioequivalence to the approved reference lyophilized product, Nucala solution for injection (BLA 125526). Refer to Section 6 Clinical Pharmacology for details of the single PK/BE study 204958.

### 8.2. Review of Safety

#### 8.2.1. Safety Review Approach

The Applicant submitted safety data from the single-dose clinical pharmacology study (Study 204958) and two actual use studies, one with the prefilled autoinjector (Study 204959) and one with the prefilled safety syringe device (Study 205667). While the overall exposure to the test drug product from these studies is small in terms of assessment of safety, the safety profile of mepolizumab is well-established. To support home use in a patient population (i.e., severe asthma) who is at greater risk of having severe allergic reactions, the Applicant was asked to provide additional analyses of hypersensitivity events that have occurred with mepolizumab in any pre- or postmarketing setting. A review of the new AI and SSD devices themselves was performed by CDRH and documented in a separate review. A review of the human factors study and IFU was performed by DMEPA and also documented in a separate review.

### 8.2.2. Review of the Safety Database

**Overall Exposure**

The overall exposure to the test drug product in three clinical studies is listed in Table 29 below. Given the short duration and unblinded, uncontrolled design of these studies, the ability to detect new, unexpected safety signals in the studies is relatively low. However, the safety profile of mepolizumab was adequately characterized in the development programs for severe eosinophilic asthma and EGPA and has been supplemented by the subsequent postmarketing experience. Given that the approved lyophilized presentation of Nucala and the proposed prefilled AI and SSD are bioequivalent, the expectation is that the safety profile will be the same.

**Table 29. Overall Exposure in Three Clinical Studies**

| Clinical Study | Study Design | Lyophilized Nucala Solution | Prefilled Autoinjector | Prefilled Safety Syringe Device |
|---|---|---|---|---|
| Clinical Pharmacology Study 204958 | Single-dose, open-label, three-arm, in healthy subjects, comparing PK between reference and prefilled autoinjector/safety syringe | 85 | 79 | 80 |
| Actual Use Study 204959 | Open-label, single-arm, self-administered Q4W for 12 weeks in patients with asthma | 0 | 159 | 0 |
| Actual Use Study 205667 | Open-label, single-arm, self-administered Q4W for 12 weeks in patients with asthma | 0 | 0 | 56 |
| Total Exposure | | 85 | 238 | 136 |

Q4W = once every 4 weeks, PK = pharmacokinetics
Source: Reviewer adapted from study reports of 204958, 204959, and 205667.

### 8.2.3. Adequacy of Applicant's Clinical Safety Assessments

**Issues Regarding Data Integrity and Submission Quality**

Data integrity and submission quality are adequate for the safety review.

**Categorization of Adverse Events**

The Applicant defined an adverse event (AE) as any untoward medical occurrence in a patient during the study; this definition did not require a causal relationship with the study drug. Investigators also reported any abnormal laboratory assessment, electrocardiogram finding, vital sign, or physical exam finding that the investigator judged to be a clinically significant worsening from baseline as adverse events.

The Applicant coded AE terms in both pivotal trials using Medical Dictionary for Regulatory Activities (MedDRA) version 20.0. Treatment-emergent AEs (TEAEs) were defined as AEs that occurred between the treatment start date and 28 days after the last dose of treatment. The Applicant defined SAEs as any untoward medical occurrence that results in death, is life-

threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, or is a congenital anomaly/birth defect. All SAEs were adjudicated by a blinded independent clinical endpoint committee. The Applicant did not reference a defined scale for grading the severity of AEs in the trial protocols; the clinical investigators determined severity grading.

**Routine Clinical Tests**

Routine clinical tests included vital signs, physical examination, electrocardiogram, hematology, and clinical chemistry tests. Clinically significant changes in the routine clinical tests were reported and described as adverse events. There were no clinically significant differences in the routine clinical tests between the study groups in the single-dose clinical pharmacology Study 204958, or between baseline and during the study in the single-arm actual use studies for the prefilled autoinjector (Study 204959) and prefilled safety syringe (Study 205667).

### 8.2.4. Safety Results

**Deaths**

There were no deaths reported in the clinical studies.

**Serious Adverse Events**

A total of 13 SAEs in eight subjects were reported in the three clinical studies. These SAEs did not reveal new safety signals for the test drug product mepolizumab autoinjector and safety syringe.

There was one SAE reported in the single-dose clinical pharmacology Study 204958. The subject took the reference drug product and reported a post-treatment SAE of atrial fibrillation that was considered not related to study treatment.

In the actual use study for the autoinjector (Study 204959), there were nine SAEs reported during the study. One subject had a road traffic accident and reported six SAEs (road traffic accident, multiple bone fractures, and chest discomfort). Reported SAEs of the other three subjects included allergic alveolitis, asthma, and pneumothorax. All SAEs were considered not related to the test drug product by the investigator.

In the actual use study for the safety syringe (Study 205667), there were three SAEs (two asthma aggravated and one diverticulitis) reported during the study. These SAEs were considered not related to the test drug product by the investigator.

**Dropouts and/or Discontinuations Due to Adverse Effects**

Two subjects dropped out due to SAEs in the actual use studies. One subject in the actual use study for the autoinjector (Study 204959) withdrew after the first dose of the treatment due to

SAEs related to a road traffic accident. One subject in the actual use study for the safety syringe (Study 205667) discontinued the study after the second dose of the treatment due to the AE of lack of efficacy and the SAE of asthma.

**Significant Adverse Events**

There were no reports of anaphylaxis nor other allergic (type I hypersensitivity) reactions in the actual use studies. There were no other significant adverse events reported in the clinical studies.

**Treatment Emergent Adverse Events and Adverse Reactions**

The incidences of TEAEs were similar in the clinical pharmacology study (34%) and in the actual use studies for the autoinjector (35%) and for the safety syringe (30%). Table 30 shows the adverse events reported in ≥3% subjects in any clinical studies. The most commonly reported AE in all studies was headache, followed by URTI, fatigue, nasopharyngitis, and urinary tract infection. Less commonlyreported AEs included injection-site reaction, rhinorrhea, wheezing, acute sinusitis, conjunctivitis, gastroenteritis viral, diverticulitis, psoriasis, rash, tachycardia, and diabetes inadequate control. The AEs reported in the studies are consistent with the known, labeled adverse effectsof mepolizumab and did not reveal new safety signals.

**Table 30. Adverse Events Reported in ≥3% Subjects in Any Clinical Studies**

| | Clinical Pharmacology Study 204958 | | | | Actual Use Studies | |
|---|---|---|---|---|---|---|
| | Lyophilized Mepolizumab (Reference) N=85 | Prefilled Autoinjector N=79 | Prefilled Safety Syringe N=80 | Total N=244 | Prefilled Autoinjector Study 204959 N=159 | Prefilled Safety Syringe Study 205667 N=56 |
| Any AE (%) | 25 (29%) | 27 (34%) | 30 (38%) | 82 (34%) | 56 (35%) | 17 (30%) |
| Headache | 6 (7%) | 9 (11%) | 8 (10%) | 23 (9%) | 8 (5%) | --- |
| URTI | 2 (2%) | 3 (4%) | 6 (8%) | 11 (5%) | 6 (4%) | 4 (7%) |
| LRTI | --- | --- | --- | --- | 5 (3%) | --- |
| Fatigue | 5 (6%) | 2 (3%) | 1 (1%) | 8 (3%) | --- | --- |
| UTI | --- | --- | --- | --- | 5 (3%) | --- |
| Asthma | --- | --- | --- | --- | --- | 2 (4%) |
| Nasopharyngitis | --- | --- | --- | --- | 9 (6%) | --- |

AE = adverse event, URTI = upper respiratory tract infection, LRTI = lower respiratory tract infection, UTI = urinary tract infection
Source: Reviewer adapted from study reports of 204958, 204959, and 205667.

**Immunogenicity**

ADA assessments were conducted for all 196 subjects in the actual use studies at baseline and 192 subjects at Week 12 (end of study). Positive ADA results were reported for a total of nine subjects (5%) at any time during the study. Of these nine subjects, seven (4%) had positive ADA at baseline and four subjects (2%) only at Week 12. There were two subjects who had positive ADA results at both baseline and Week 12. All subjects with positive ADA tested negative for NAbs. The level of mepolizumab ADA formation in these studies is similar to that observed in previous clinical trials, which was 6% of patients with asthma who received Nucala 100-mg treatment according to the approved Nucala labeling. The clinical relevance of the presence of anti-mepolizumab antibodies is not known, but did not appear to be associated with

hypersensitivity events. The low incidence of the positive ADA test in the actual use studies in this submission did not reveal a new safety signal.

### 8.2.5. Analysis of Submission-Specific Safety Issues

Any pain at the injection site was assessed by the subject using a visual analog scale (VAS) from 0 (no pain) to 100 (worst imaginable pain) immediately after injection, 1-hour post-injection, and 24 hours post-injection. Table 24 and Table 28 show the assessment of the pain at injection site of the autoinjector and safety syringe, respectively. In general, subjects reported pain at VAS scores of around 10 out of 100, on average, immediately after the initial self-injection, and the pain VAS scores dropped at 1 hour after self-injection and 24 hours after self-injection (averaged VAS scores of 2 to 3 out of 100). Subjects also reported lower pain VAS scores at the second and third self-injections (Weeks 4 and 8, respectively) than at the first self-injection (Week 0).

There were no reports of incidents or malfunctions associated with the autoinjector and safety syringe in the studies. However, there were a few reports of withdrawing the autoinjector needle too early in Study 204959, which may be related to the relatively long injection time.

### 8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

Patient-reported clinical outcome data for actual use studies were informative to tolerability of the proposed Nucala injection prefilled autoinjector and safety syringe. Exit interviews of subjects revealed positive perceptions overall.

### 8.2.7. Safety Analyses by Demographic Subgroups

The number of subjects by demographic subgroups are relatively small (Table 31). There were 11 (7%) and 2 (4%) adolescents in actual use studies with the AI and SSD, respectively. No significant differences were reported between adolescents and other subjects with regard to the self-administration by subjects or their caregivers and the responses in pain and satisfactory evaluations. There were no specific safety signals identified for demographic subgroups in this submission.

**Table 31. Subject Demographics of All Clinical Studies for BLA 761122**

| | Clinical Pharmacology Study 204958 | | | | Actual Use Studies | |
|---|---|---|---|---|---|---|
| | Lyophilized Mepolizumab (Reference) N=85 | Prefilled Autoinjector N=79 | Prefilled Safety Syringe N=80 | Total N=244 | Prefilled Autoinjector Study 204959 N=159 | Prefilled Safety Syringe Study 205667 N=56 |
| Gender (%) | | | | | | |
| F | 40 (47) | 36 (46) | 38 (48) | 114 (47) | 98 (62) | 33 (59) |
| M | 45 (53) | 43 (54) | 42 (52) | 150 (53) | 61 (38) | 23 (42) |
| Age, Years (%) | | | | | | |
| Mean (SD) | 46.1 (15.1) | 46.5 (15.0) | 47.5 (14.9) | 46.7 (15.0) | 49.3 (16.2) | 50.8 (13.0) |
| 12–17 | --- | --- | --- | --- | 11 (7) | 2 (4) |
| 18–64* | 73 (86) | 67 (85) | 69 (86) | 209 (86) | 122 (77) | 47 (84 |
| ≥65 | 12 (14) | 12 (15) | 11 (14) | 35 (14) | 26 (16) | 7 (13) |
| Ethnicity (%) | | | | | | |

| | Clinical Pharmacology Study 204958 | | | | Actual Use Studies | |
|---|---|---|---|---|---|---|
| | Lyophilized Mepolizumab (Reference) N=85 | Prefilled Autoinjector N=79 | Prefilled Safety Syringe N=80 | Total N=244 | Prefilled Autoinjector Study 204959 N=159 | Prefilled Safety Syringe Study 205667 N=56 |
| Hispanic/Latino | 3 (4) | 3 (4) | 2 (3) | 8 (3) | 11 (7) | 0 |
| Not Hispanic/ Latino | 82 (96) | 76 (96) | 78 (98) | 236 (97) | 148 (93) | 56 (100) |
| Race (%) | | | | | | |
| White/Caucasian | 64 (75) | 61 (77) | 62 (78) | 187 (77) | 126 (79) | 45 (80) |
| African American | 18 (21) | 15 (19) | 18 (23) | 51 (21) | 25 (16) | 8 (14) |
| Asian | 1 (1) | 1 (1) | 0 | 2 (1) | 6 (4) | 1 (2) |
| Others | 2 (2) | 2 (2) | 0 | 4 (2) | 2 (1) | 2 (4) |

*In clinical pharmacology Study 204958, age groups are 19 to 64 and ≥65 years.
SD = standard deviation
Source: Reviewer adapted from study reports of 204958, 204959, and 205667.

### 8.2.8. Specific Safety Studies/Clinical Trials

No specific safety studies or clinical trials were performed for this submission.

### 8.2.9. Additional Safety Explorations

**Human Carcinogenicity or Tumor Development**

Human carcinogenicity or tumor development was not specifically assessed or required for this submission.

**Human Reproduction and Pregnancy**

Human reproduction and pregnancy were not specifically assessed or required for this submission. No pregnancies were reported during the 12-week actual use studies.

**Pediatrics and Assessment of Effects on Growth**

No assessment of pediatrics or assessment of effects on growth were performed or required for this submission.

**Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

No assessments of overdose, drug abuse potential, withdrawal, and rebound were performed or required for this submission.

**Home Use**

The proposed labeling for Nucala injection prefilled AI and SSD allow for self/caregiver administration and home use. Because patients with severe asthma are at high risk with respect to hypersensitivity reactions and potential bronchospasm, the Applicant was asked to provide an analysis of hypersensitivity events (including anaphylaxis) from the clinical development

program for mepolizumab and from post-marketing experience to support home use of Nucala injection prefilled AI and SSD in the indicated patient population.

On April 17, 2019, the Applicant submitted a summary of events of anaphylaxis and systemic allergic/hypersensitivity reactions reported across mepolizumab clinical programs and postmarketing. In the mepolizumab clinical development program, a total of 1878 patients with severe asthma, 1510 patients with COPD, and 68 patients with EGPA participated in placebo-controlled clinical studies. Consistent with the individual clinical study reports/integrated summaries, the incidence of systemic allergic/hypersensitivity reactions was low and similar between mepolizumab and placebo groups with no apparent dose effect. Twenty-one subjects (0.99%) on mepolizumab and 13 subjects (0.93%) on placebo reported at least one systemic allergic/hypersensitivity reaction in the integrated placebo-controlled trials in severe asthma, integrated placebo-controlled trials in COPD, and a placebo-controlled trial in EGPA. The pattern of exposure to mepolizumab and placebo prior to first systemic allergic/hypersensitivity reaction report was similar. Among those systemic allergic/hypersensitivity reactions, 12/21 (57%) and 10/13 (77%) cases were reported with the first 3 doses of mepolizumab or placebo, respectively. Seven of 21 subjects (33%) on mepolizumab reported onset of the first event within the first 60 minutes of the dose, with an additional 5 subjects (24%) reporting onset after 1 hour and within 24 hours of exposure. Similarly, 3/13 (23%) subjects on placebo reported onset of the first event within the first 60 minutes of the dose, with an additional 5 subjects (39%) reporting onset after 1 hour and within 24 hours of exposure. All of these allergic/hypersensitivity reactions were non-serious except for one event on mepolizumab and 3 events in the placebo group. None of the reports in the mepolizumab group were considered to meet NIAID/FAAN (Sampson's) criteria for anaphylaxis by the investigator.

A search of post-marketing data revealed 77 reports of mepolizumab and anaphylaxis. On medical review of the 77 cases by GSK, 18 cases were considered to meet NIAID/FAAN (Sampson’s) criteria for anaphylaxis, 20 cases did not meet the criteria, and 39 cases could not be assessed due to limited relevant clinical information provided.

The Warnings and Precautions section of the current and proposed Nucala prescribing information includes that hypersensitivity reactions may occur with SC mepolizumab administration. Though not powered for safety, the two actual use studies included in this submission did not report any hypersensitivity reaction events following home use for 12 weeks.

Overall, the rate of hypersensitivity reactions for mepolizumab appears to be relatively low. Furthermore, changes in the presentation (lyophilized to prefilled AI or SSD) and person administering the drug (healthcare provider vs self or caregiver) are not expected to increase the risk of systemic hypersensitivity reactions. Therefore, allowing physicians to determine which patients may transition to home use with the AI or SSD following adequate training appears reasonable.

### 8.2.10. Safety in the Postmarket Setting

**Safety Concerns Identified Through Postmarket Experience**

The Applicant submitted a descriptive summary of safety data from postmarketing sources with a cut-off date of March 23, 2018. As of the cut-off date, Nucala is approved in the United States (approved on November 4, 2015), all European Economic Area countries, Japan, and more than 20 other countries for add-on maintenance treatment for patients with severe eosinophilic asthma at a dose of 100-mg SC every 4 weeks. On December 12, 2017, Nucala was approved in the United States for the treatment of adult patients with EGPA at a dose of 300 mg every 4 weeks.

The cumulative exposure to Nucala in the postmarketing setting is estimated to be 23,343.85 patient years. The postmarketing experience shows that the safety profile of Nucala remains generally consistent with the safety profile observed in the clinical trial setting. The most frequently reported AEs from postmarketing sources are asthma, headache, and dyspnea. Following a review of spontaneous postmarketing reports of anaphylaxis, the mepolizumab label was updated to include "anaphylaxis" in the existing Warnings and Precautions section of the prescribing information.

The postmarketing safety of mepolizumab has been assessed in three reviews by the Division of Pharmacovigilance I (DPV-I) in the Office of Surveillance and Epidemiology:

- On October 10, 2017, DPV-I completed a Postmarket Drug Surveillance Summary for mepolizumab. DPV-I performed an analysis of the FDA Adverse Event Reporting System (FAERS) database, including a disproportionality analysis using Empirical Signal, and the medical literature and reviewed preapproval clinical data and periodic safety reports to determine new safety signals with mepolizumab. Herpes zoster was identified in clinical trials and included in initial mepolizumab product labeling, and likewise, DPV-I identified 44 unique reports of herpes zoster in the FAERS database from November 4, 2015, (U.S. approval date) to July 31, 2017. DPV-I recommended close monitoring of the signal of herpes zoster.
- On December 15, 2017, DPV-I completed a Pediatric Postmarketing Pharmacovigilance Review for mepolizumab. DPV-I evaluated all pediatric adverse event reports with mepolizumab in the FAERS database from November 4, 2015, (U.S. approval date) to July 31, 2017. The review of the FAERS reports identified two non-fatal cases of the unlabeled adverse events of histiocytic necrotizing lymphadenitis and varicella infection; however, no new safety signals were identified with mepolizumab in pediatric patients after review of the cases.
- Most recently, on July 12, 2018, DPV-I evaluated available postmarketing data in the FAERS database and medical literature for an association between potential safety signals of acute pancreatitis, supraventricular tachyarrhythmias, gastrointestinal hemorrhage, and embolic and thrombotic events with mepolizumab use from November 4, 2015, (U.S. approval date) to April 4, 2018. This review was prompted by exploratory safety analyses of any dose of mepolizumab versus placebo in a COPD study that identified imbalances in the proportion of subjects experiencing SAEs or AEs classified

as supraventricular tachyarrhythmia, cardiovascular thrombotic events, gastrointestinal bleeding, and acute pancreatitis. A search in the FAERS database identified 36 cases of acute pancreatitis (four cases), supraventricular tachyarrhythmias (seven cases), gastrointestinal hemorrhage (six cases), and embolic and thrombotic events (19 cases) associated with mepolizumab use. A search of the medical literature identified zero cases. No postmarketing safety signals were identified after review of the limited number of cases identified in the FAERS database because the cases lacked sufficient information to determine the contribution of mepolizumab to the event. DPV-I recommended to continue routine pharmacovigilance monitoring for mepolizumab.

**Expectations on Safety in the Postmarket Setting**

The safety profile of the proposed Nucala injection prefilled autoinjector and safety syringe in postmarketing setting is expected to be similar to the approved Nucala injection product.

### 8.2.11. Integrated Assessment of Safety

The Applicant submitted three clinical studies to the BLA: a single-dose clinical pharmacology study in healthy volunteers, and two actual use studies for the prefilled autoinjector and safety syringe in patients with severe eosinophilic asthma. A total of 238 subjects (79 healthy volunteers and 159 patients with asthma) were exposed to the prefilled autoinjector, and 136 subjects (80 healthy volunteers and 56 patients with asthma) were exposed to the prefilled safety syringe device. Although the safety database is limited by the short duration and unblinded, uncontrolled design of these studies, no new safety signals were observed. That being said, the safety profile of mepolizumab was adequately characterized in the development programs for severe eosinophilic asthma and EGPA and has been supplemented by the subsequent postmarketing experience. Given that the approved lyophilized presentation of Nucala and the proposed prefilled AI and SSD are bioequivalent, the expectation is that the safety profile will be the same. Exposure to the new device presentations appears adequate given that no substantial issues were identified related to device function or ability to use/handle the devices.

While the potential risk for hypersensitivity events (including anaphylaxis) is a concern with any biologic, patients with severe asthma may be at higher risk for severe reactions due to bronchial hyper-reactivity. To support proposed labeling which allows for self or caregiver administration of mepolizumab via the AI or SSD, the Applicant provided an analysis of hypersensitivity reactions reported across mepolizumab clinical development programs and from post-marketing experience. A review of the data showed a low frequency of hypersensitivity events overall, and even lower frequency of severe systemic reactions/anaphylaxis. Furthermore, the timing of events suggests that events primarily occur within the first three exposures. Provided patients receive adequate education and training, the benefit of having a more convenient presentation for home use outweighs the small risk of severe allergic reactions. As hypersensitivity reactions are currently labeled as a Warnings and Precaution in the Nucala prescribing information, this review concludes that this potential risk in a severe asthma population may be mitigated through labeling which states that physicians should determine the appropriateness of self-administration following proper training in injection technique.

### 8.3. Statistical Issues

None.

### 8.4. Conclusions and Recommendations

The Applicant submitted BLA 761122 for new liquid formulation presentations of Nucala (mepolizumab) in prefilled autoinjector (AI) and safety syringe devices (SSD). Nucala (mepolizumab) is currently approved as a lyophilized powder in a single-dose vial for reconstitution under BLA 125526. The Applicant seeks the same dosages, route of administration (SC), and indications for the new prefilled AI and SSD. To support the safety and effectiveness of the proposed AI and SSD presentations, the Applicant submitted a clinical pharmacology PK/BE study, two actual use studies with the AI and SSD in patients with severe eosinophilic asthma and a human factors study along with data to support the product quality and device reviews. Clinical pharmacology study 204958 demonstrated bioequivalence between the liquid formulation AI and SSD presentations and the approved lyophilized powder presentation of Nucala. Safety data from the clinical pharmacology study and actual use studies 204959 and 205667 revealed no new safety signals, device malfunction/failures, or significant issues with administration technique and was consistent with the known safety profile of mepolizumab which has been well-established in the clinical development programs for asthma EGPA, and COPD and in the postmarketing setting. The risk of hypersensitivity reactions is low and may be mitigated through labeling to allow self/caregiver administration of the AI or SSD outside a monitored clinic setting. Therefore, the overall risk/benefit assessment of the new liquid formulation presentations of Nucala (mepolizumab) in prefilled autoinjector and safety syringe devices for self/caregiver administration and home use is favorable.

The recommended action from the clinical perspective is Approval.

## 9 Advisory Committee Meeting and Other External Consultations

A Pulmonary and Allergy Drug Advisory Committee Meeting was deemed unnecessary for this BLA submission.

## 10 Pediatrics

Nucala is approved under BLA 125526 for use (1) in adults and adolescents 12 years of age and older with severe asthma, and with an eosinophilic phenotype and (2) in adults with EGPA. The Applicant is seeking the same dosages, route of administration (SC), and indications for the new SSD and AI presentations as the approved lyophilized product.

The pediatric assessment for patients 12 to 17 years of age with severe asthma with eosinophilic phenotype was fulfilled by studies supporting the safety and efficacy of the original approval of

the lyophilized drug product. The Applicant has provided adequate data to bridge the lyophilized drug product to the new liquid SSD and AI presentations, and therefore, no additional data is required to support the use of the liquid formulations in adolescent patients with asthma with eosinophilic phenotype.

The currently approved asthma and EGPA indications and age ranges for the lyophilized product are applicable to the new liquid SSD and AI presentations. The Applicant has already received a partial waiver for age group less than 6 years of age for the approved lyophilized presentation for the indication of severe eosinophilic asthma and is requesting a similar partial waiver for the new liquid formulations.

For the pediatric patient population 6 to 11 years of age, there are two deferred pediatric studies as described in the agreed initial Pediatric Study Plan and in the Approval Letter for Nucala for injection (BLA 125526) dated on November 4, 2015. The two deferred pediatric studies in patient population 6 to 11 years of age are applicable to the new liquid SSD and AI presentations. The 2 study reports were submitted under BLA 125526/S-012 on November 16, 2018 and are currently under review.

- Study 2979-1: Conduct a 12-week, randomized, open-label, pharmacokinetic, and pharmacodynamics study of Nucala (mepolizumab) in pediatric patients with asthma 6 years to 11 years of age (Part A of Study 200363). Final report submission: September 2019.
- Study 2979-2: Conduct a 12-month long-term safety and pharmacodynamics extension study of Nucala (mepolizumab) in pediatric patients with asthma 6 years to 11 years of age (Part B of Study 200363). Final report submission: September 2019.

EGPA has orphan designation and is therefore exempted from Pediatric Research Equity Act requirements.

# 11 Labeling Recommendations

## 11.1. Prescription Drug Labeling

**Prescribing Information**

The Applicant proposes to use the same product labeling for all mepolizumab products, including the approved Nucala for injection (BLA 125526) and the new liquid formulation SSD and AI presentations. The prescribing information is basically the same as the approved Nucala for injection labeling with revisions in Section 2 DOSAGE AND ADMINISTRATION and Section 16 HOW TO SUPPLIED/STORAGE AND HANDLING to include additional information regarding the new liquid formulation SSD and AI presentations. Patient Information is also revised accordingly. Two new Instructions for Use (IFUs) were submitted for the AI and SSD presentations.

The Division of Medication Error, Prevention, and Analysis (DMEPA) reviewed the Human Factors validation study and determined that the results were acceptable to support the proposed IFUs. In addition, DMEPA determined that applying the same root name Nucala for the new AI and SSD presentations was acceptable. The CDER/CBER Biosimilar Implementation Committee determined that a suffix in the mepolizumab nonproprietary name was not needed in this particular case, and if used, may create confusion since lyophilized mepolizumab was approved prior to the naming convention and does not currently have a suffix in the nonproprietary name.

Recommendations from labeling consultants in DMPP, OPDP, Patient Labeling Team were incorporated into the final label. The labeling negotiation is ongoing and the agreed upon labeling, including the Patient Information and Instructions for Use, will be filed separately.

## 12 Risk Evaluation and Mitigation Strategies

None

## 13 Postmarketing Requirements and Commitment

There is a postmarketing commitment (PMC) to address the quality CMC issue: To conduct a microbial retention study using mepolizumab drug product under conditions that do not impact viability of the challenge organism. The study will assess how (b) (4) Final reporting submission time: October 31, 2019. Refer to separate product quality microbiology review of the drug substance and drug product for more detail.

## 14 Deputy Division Director (DPARP) Comments

This biologics license application (BLA) (761122) is for new liquid formulation presentations of Nucala (mepolizumab) in a prefilled safety syringe device (SSD) and autoinjector (AI). The Applicant is seeking the same dosages, route of administration (SC), and indications for the new SSD and AI presentations as the approved lyophilized drug product [add-on treatment of severe asthma with eosinophilic phenotype in patients ≥12 years of age and for treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA)].

To support the clinical safety and effectiveness of the proposed Nucala prefilled AI and SSD, the development program relied primarily on the demonstration of bioequivalence (BE) between the approved lyophilized Nucala for injection and the proposed AI and SSD liquid formulation presentations. Study 204958 demonstrated bioequivalence between the new presentations and the approved lypophylized drug product. In addition, the application included two actual use studies to evaluate administration of the prefilled AI and SSD outside the clinic setting (i.e.,

home use with administration by the patient or caregiver). All subjects successfully self-administered or administered by caregivers with the proposed liquid drug product prefilled AI or SSD.

The safety profile of mepoluzimab was adequately characterized in the the original development programs for severe asthma with an eosinophilic phenotype and EGPA, and is supplemented by the subsequent post-marketing experience. A total of 238 subjects were exposed to the prefilled AI, and 136 subjects wre exposued to the prefilled SSD. While these were short duration/unblinded studies, no new safety signals were noted. Given the demonstration of bioequivalence, a similar safety profile is expected with the new presentations. No safety issues were identified with respect to device function.

To support proposed labeling which allows for self or caregiver administration of mepolizumab via the AI or SSD outside a healthcare setting, the Applicant provided an analysis of hypersensitivity reactions reported across mepolizumab clinical development programs and from post-marketing experience. Based on the review of the data (low frequency of hypersensitivity events overall, and even lower frequency of severe systemic reactions/anaphylaxis, timing of events, etc), I agree with the clinical reviewers' assessment that the benefit of having a more convenient presentation for home use outweighs the small risk of severe allergic reactions, that this risk can be mitigated through labeling, which states that physicians should determine the appropriateness of self-administration following proper training in injection technique.

In summary, the data support approval of the two new liquid presentations of mepoluzimab in the AI and SSD. I concur with the recommendations for approval from the various review disciplines. The regulatory action for BLA 761122 is *Approval.*

APPEARS THIS WAY ON ORIGINAL

# 15 Appendices

## 15.1. References

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## 15.2. Financial Disclosure

**Covered Clinical Study (Name and/or Number): Studies 204958, 204959, and 205667**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 210 (27 investigators for Study 204958, 139 investigators for Study 204959, and 44 investigators for Study 205667) | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): None | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):<br>None | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: _____<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in S<br>Sponsor of covered study: _____ | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☐ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☐ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3): None | | |
| Is an attachment provided with the reason: | Yes ☐ | No ☐ (Request explanation from Applicant) |

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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BANU A KARIMI SHAH
06/03/2019 09:08:21 PM
Signing with the delegated authority of Dr. Sally Seymour, Acting Division Director, DPARP